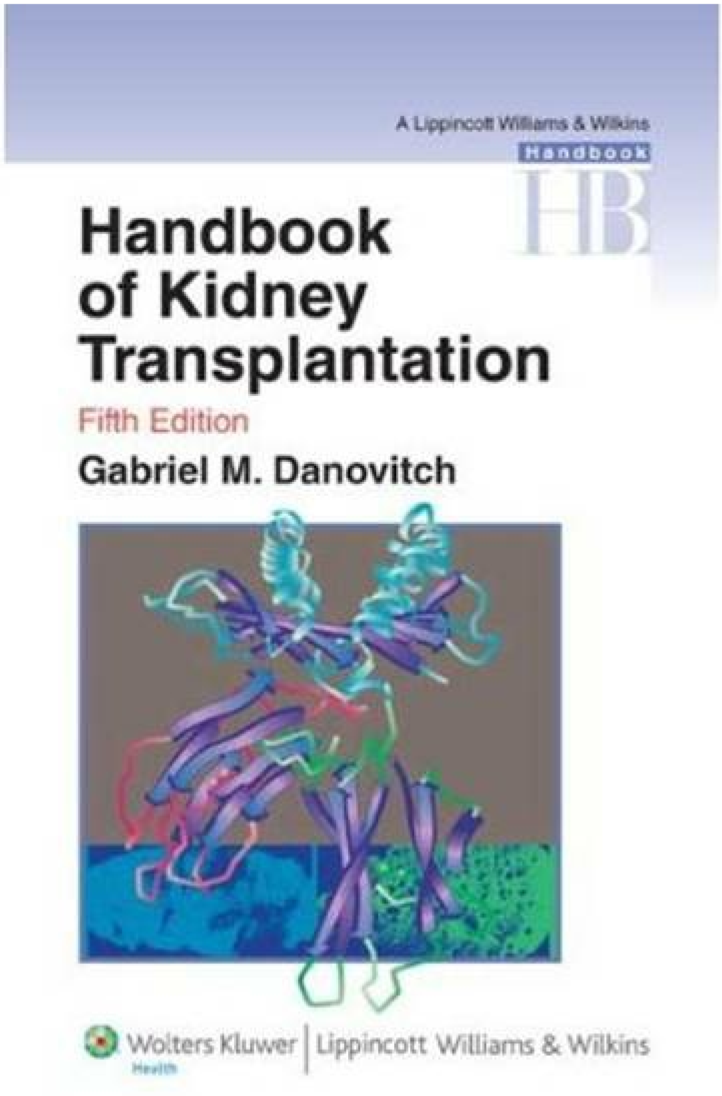
Handbook of Kidney Transplantation
5th Edition



- **Edition:** Fifth Edition edition (October 1, 2009)
- **Publisher:** Lippincott Williams & Wilkins
- **Language:** English
- **ISBN-10:** 0781793742
- **ISBN-13:** 978-0781793742

Editor

Gabriel M. Danovitch MD
Medical Director, Kidney and Pancreas Transplant Program
UCLA Medical Center;
Professor, Department of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California

CONTRIBUTORS

Suphamai Bunnapradist MD
Director of Research, Kidney and Pancreas Transplant Program
Professor
Department of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California

J. Michael Cecka PhD
Professor
Department of Pathology and Laboratory Medicine
David Geffen School of Medicine at UCLA;
Director of Clinical Research
University of California, Los Angeles Immunogenetics Center
Los Angeles, California

Arthur H. Cohen MD
Professor
Department of Pathology and Medicine
David Geffen School of Medicine at
University of California, Los Angeles;
Director
Department of Renal Pathology
Cedars-Sinai Medical Center
Los Angeles, California

Gabriel M. Danovitch MD
Medical Director, Kidney and Pancreas Transplant Program
UCLA Medical Center;
Professor, Department of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California

Itai Danovitch MD
Director, Addiction Psychiatry Clinical Services
Assistant Professor, Department of
Psychiatry and Neurobehavioral Sciences
David Geffen School of Medicine at UCLA
Cedars-Sinai Medical Center
Los Angeles, California

Francis L Delmonico MD
Director of Medical Affairs
The Transplantation Society
World Health Organization
Advisory for Human Transplantation
Professor of Surgery Harvard Medical School
Massachusetts General Hospital
Medical Director
New England Organ Bank
Boston, Massachusetts

Robert B. Ettenger MD
Chief, Pediatric Nephrology
Director, Renal Transplantation Service
Professor, Department of Pediatrics
Mattel Children's Hospital at UCLA
Los Angeles, California

Fabrizio Fabrizi MD
Staff Nephrologist
Division of Nephrology and Dialysis
Maggiore Hospital
Milan, Italy

Aric L Gregson MD
Assistant Professor

Department of Medicine
Division of Infectious Diseases
David Geffen School of Medicine at UCLA
Los Angeles, California

H. Albin Gritsch MD
Surgical Director, Kidney and Pancreas Transplant Program
Professor, Department of Urology
David Geffen School of Medicine at UCLA
Los Angeles, California

Jeffrey P. Kahn PhD, MPH
Professor
Director and Maas Family Chair in Bioethics
Center for Bioethics
University of Minnesota
Minneapolis, Minnesota

Bertram L Kasiske MD
Professor
Department of Medicine
Division of Renal Diseases and Hypertension
University of Minnesota Medical School
Minneapolis, Minnesota

Bernard M. Kubak MD, PhD
Professor
Department Medicine/Infectious Diseases
David Geffen School of Medicine at UCLA
Los Angeles, California

John Leppert MD
Assistant Professor
Department of Urology
Stanford University School of Medicine
Stanford, California

Gerald S. Lipshutz MD, MS
Associate Professor
Director, Pancreas Transplant Program

Departments of Surgery and Urology
David Geffen School of Medicine at UCLA
Los Angeles, California

Didier A. Mandelbrot MD
Associate Professor
Department of Medicine
Harvard Medical School;
Director of Living Kidney Donor Program
Department of Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Cynthia L. Maree MD
Attending Physician
Department of Medicine
Division of Infectious Diseases
Cedars Sinai Medical Center
Los Angeles, California

Paul Martin MD
Chief, Division of Hepatology
Center for Liver Diseases
Leonard M. Miller School of Medicine at the University of Miami
Miami, Florida

Cynthia C. Nast MD
Professor
Department of Pathology
David Geffen School of Medicine at UCLA;
Associate Director
Department of Renal Pathology
Cedars-Sinai Medical Center
Los Angeles, California

Kevin J. O'Connor MS
Senior Vice-President
New England Organ Bank
Boston, Masachusetts

Allison L Pearl MD
Abdominal Fellow
Department of Diagnostic Radiology
David Geffen School of Medicine at UCLA
Los Angeles, California

David A. Pegues MD
Professor of Clinical Medicine
Division of Infectious Diseases
David Geffen School of Medicine at UCLA
Los Angeles, California

Thu Pham MD
Associate Professor
Director of Outpatient Services
Kidney Transplant Program
Department of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California

Nagesh Ragavendra MD
Professor
Department of Radiological Sciences
David Geffen School of Medicine at UCLA
Los Angeles, California

Raja Rajalingam PhD
Assistant Professor, Department of Pathology
University of California, Los Angeles Immunogenetics Center
David Geffen School of Medicine at UCLA
Los Angeles, California

Elaine F. Reed PhD
Professor
Department of Pathology and Laboratory Medicine
Director, UCLA Imunogenetics Center
David Geffen School of Medicine of UCLA
Los Angeles, California

Mara Hersh Rifkin

Clinical Social Worker
Department of Medical Center Care Coordination
Kidney and Pancreas Transplant Program
Los Angeles, California

Mohamed H. Sayegh MD
Warren E. Grupe and John P. Merrill Chair in Transplantation Medicine
Professor of Medicine and Pediatrics
Harvard Medical School;
Director, Schuster Family Transplantation Research Center
Brigham and Women's Hospital & Children's Hospital Boston
Boston, Massachusetts

Christiaan Schiepers MD, PhD
Professor
Molecular & Medical Pharmacology
David Geffen School of Medicine at UCLA
Los Angeles, California

Peter Schulam MD
Chief, Minimally Invasive Surgery
Professor of Urology
The Department of Urology
David Geffen School of Medicine at UCLA
Los Angeles, California

Jennifer S. Singer MD
Assistant Professor
Department of Urology
David Geffen School of Medicine at UCLA
Los Angeles, California

Eileen W. Tsai MD
Assistant Professor of Pediatrics
Department of Pediatrics
David Geffen School of Medicine at UCLA
Los Angeles, California

Jeffrey L. Veale MD
Assistant Professor

Department of Urology
Director, Paired Donation Program
David Geffen School of Medicine at UCLA
Los Angeles, California

Susan Weil RD, CSR
Renal Dietitian
Kidney Transplant Program
David Geffen School of Medicine at UCLA
Los Angeles, California

Alan Wilkinson MD
Medical Director, Kidney and Pancreas Transplant Program
UCLA Medical Center;
Professor, Department of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California

Jennifer Zhang MD
Assistant Professor, Department of Pathology
University of California, Los Angeles Immunogenetics Center
David Geffen School of Medicine at UCLA
Los Angeles, California

Dedication

In honor of my mother, Gertrude Danovitch, now nearly a hundred years old, who left her village in Poland as a young child to grow up in Cardiff, Wales and thus escaped the conflagration that was to engulf her family and community.

PREFACE

The modern era of transplantation can be said to have begun with two momentous events in the early 1950s. In 1953, Peter Medawar and his colleagues at University College, London described actively acquired immunologic tolerance in rats, thus heralding the science of transplant immunology and an ongoing search for a similar, reproducible phenomenon in humans. The modern era of clinical transplantation began on December 23, 1954, when Joseph Murray and his colleagues at Harvard performed the first kidney transplantation between identical twin brothers. Both these pioneers were rewarded with the Nobel Prize for their contributions.

In many ways, the promise of these discoveries has been fulfilled in the half century that has followed. The mere fact that organ transplantation is the subject of a handbook such as this reflects the extent to which it has become normative medical practice. Hundreds of thousands of lives have been saved, and quality years have replaced years of suffering.

Our understanding of the complex immunobiology of the immune response has advanced and has brought widespread benefits well beyond the field of organ transplantation. A broad armamentarium of immunosuppressive medications is now available, and innovative surgical techniques serve to expand the donor pool and minimize morbidity. National and international organ-sharing organizations are an accepted part of the medical landscape of the developed world.

Modern organ transplantation can be visualized as a complex edifice that rests on a triangular base. In one corner is the basic research that is the life-blood of improvement and innovation. Nowhere in medicine is the term *translational medicine* more relevant or does research reach the bedside with greater speed. In another corner is clinical transplant medicine, a new medical subspecialty that requires compulsive, detail-oriented clinical care and both organ-specific and broad expertise. In the third corner are the ethical and cultural underpinnings of the whole transplantation endeavor, an endeavor that is utterly dependent on a well-developed sense of shared humanity and community and on absolute trust among medical staff, patients, and families that is the bed-rock of societal acceptance of organ donation, from both the living and the dead.

The edifice is strong, but its strength cannot be taken for granted. The immune system still has many secrets it has yet to reveal. As this text describes, the ultimate goal of

donor-specific tolerance, either complete or near complete, appears “near, but yet so far.” Clinical xenotrans-plantation, a procedure that promised to provide the ultimate answer to the organ donor shortage, remains remote. The availability of new immunosuppressive agents has permitted the introduction of innovative immunosuppressive regimens designed to minimize toxicity. Yet the success of clinical transplantation—with low mortality, high graft survival, and a low incidence of rejection episodes—has, paradoxically, made it more difficult to prove the benefit of new approaches. Because the demand for organs greatly outstretches supply, patients with advanced kidney disease who do not have a living donor may be faced with an interminable, and often morbid, wait for an organ from a deceased donor. The need for living donors has, on the one hand, provided a stimulus to develop ingenious new techniques and approaches to facilitate donation, and on the other hand, spawned an illegal, exploitive, global market in purchased organs. The Declaration of Istanbul on Organ Trafficking and Transplant Tourism (see Appendix) serves to codify the protection of the health and welfare of living donors while promoting the effective and healthy practice of deceased donation all over the globe.

The 4-year intervals between the publication of each of the editions of the *Handbook of Kidney Transplantation* are a reflection of the rate of change in the world of organ transplantation. This fifth edition has been thoroughly updated and revised to reflect the most current knowledge and practice in the field. Like its predecessors, its mission is to make the clinical practice of kidney transplantation fully accessible to all those who are entrusted with the care of our long-suffering patients.

Gabriel M. Danovitch
October 2009

1

Options for Patients with End-Stage Renal Disease

Gabriel M. Danovitch

Before 1970, therapeutic options for patients with end-stage renal disease (ESRD) were quite limited. Only a small number of patients received regular dialysis because few dialysis facilities had been established. Patients underwent extensive medical screening to determine their eligibility for ongoing therapy, and treatment was offered only to patients who had renal failure as the predominant clinical management issue. Kidney transplantation was in the early stages of development as a viable therapeutic option. Transplant immunology and immunosuppressive therapy were in their infancy, and for most patients, a diagnosis of chronic renal failure was a death sentence.

In the decades that followed, the availability of care for patients with kidney failure grew rapidly throughout the developed world. In the United States, the passage of Medicare entitlement legislation, in 1972, to pay for renal replacement therapy (RRT—maintenance dialysis and renal transplantation), provided the major stimulus for this expansion. In the so-called developed world, RRT services are now available, in principle if not always in practice, for all those in need. In the developing world, such services are still sporadic. It has been estimated that in South Asia, more than 90% of patients with ESRD die within months of diagnosis, and in most parts of Africa, the reality is even starker.

Despite numerous medical and technical advances, patients with kidney failure who are treated with dialysis often remain unwell. Constitutional symptoms of fatigue and malaise persist despite better management of anemia with erythropoietin. Progressive cardiovascular disease (CVD), peripheral and autonomic neuropathy, bone disease, and sexual dysfunction are common, even in patients who are judged to be treated adequately with dialysis. Patients may become dependent on family members or others for physical, emotional, and financial assistance. Rehabilitation, particularly vocational rehabilitation, remains poor. Such findings are not unexpected, however, because the most efficient hemodialysis regimens provide less than 15% of the small-solute removal of two normally functioning kidneys. Removal of higher-molecular-weight solutes is even less efficient.

For most patients with kidney failure, kidney transplantation has the greatest potential

for restoring a healthy, productive life. Renal transplantation does not, however, occur in a clinical vacuum. Virtually all transplant recipients have been exposed to the adverse consequences of chronic kidney disease (CKD). Practitioners of kidney transplantation must consider the clinical impact of CKD on the overall health of renal transplantation candidates when this therapeutic option is first considered. They must also remain cognizant of the potential long-term consequences of previous and current CKD (see Chapter 7) during what may be decades of clinical follow-up after successful renal transplantation (see Chapter 10). For updated reviews of the medical literature relating to ESRD and dialysis and transplantation, readers are referred to the American Society of Nephrology Self-Assessment Program (NephSAP) (see "Selected Readings").

STAGES OF CHRONIC KIDNEY DISEASE

Table 1.1 summarizes the stages of CKD as defined by the National Kidney Foundation Disease Outcome Quality Initiative (K/DOQI). The purpose of this classification is to permit more accurate assessments of the frequency and severity of CKD in the general population, enabling more effective targeting of treatment recommendations. Note that the classification is based on estimated values for glomerular filtration rate (GFR) and that the terms *kidney failure* and *ESRD are* used for patients with values less than 15 mL per minute. It has been estimated that close to 20 million adults in the United States have CKD that can be categorized as stage 1, 2, 3, or 4, whereas nearly half a million have overt kidney failure, or stage 5 CKD. The classification may overestimate the incidence of CKD in elderly people because of the impact of normal aging on renal function. The known population of patients with ESRD thus represents only the "tip of the iceberg" of progressive CKD. It is also evident from Table 1.1 that most, if not all, kidney transplant recipients can be regarded as having some degree of CKD because their kidney function is rarely normal.

A discussion of the management of CKD in the general population is beyond the scope of this text. Strict blood pressure control and the use of angiotensin-converting enzyme inhibitors and receptor blockers, both in diabetic patients and those with proteinuria from other glomerular diseases, are standard practice. There is less certainty, however, about the benefits of these agents in patients without significant proteinuria. Low-protein diets may delay the onset of kidney failure or death in patients with established CKD, but there is insufficient evidence to recommend restricting dietary protein intake to less than 0.8 g/kg per day on a routine basis, and malnutrition is a real concern (see Chapter 19). Lipid-lowering agents and lifestyle changes, particularly smoking cessation, may slow disease progression. Many of the concerns and treatment recommendations pertaining to the long-term management of kidney transplant recipients, which are discussed in Chapter 10, also apply to patients with CKD.

Estimation of Glomerular Filtration Rate

Measurements of GFR provide an overall assessment of kidney function in both the

transplantation and nontransplantation settings. The GFR is measured best by the clearance of an ideal filtration marker such as inulin or with radiolabeled filtration markers (see Chapter 13). In clinical practice, GFR is usually estimated from measurements of creatinine clearance or serum creatinine levels to circumvent the need for timed urine specimen collections. Several equations have been developed to estimate GFR after accounting for variations in age, sex, body weight, and race. The most popular and easiest to use among Stages of Chronic Kidney Disease

---

these are the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations. The Cockcroft-Gault equation is as follows:

TABLE 1.1 Stages of Chronic Kidney Disease

Stage	Description	GFR ($mL/min/1.73m^2$)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mild decrease in GFR	60-90
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 or dialysis

GFR, glomerular filtration rate.

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ for females}$$

MDRD uses a formula based on serum creatinine, age, gender, and race. These equations were validated in studies of white patients with nondiabetic CKD. Their validity in other populations, including renal transplant recipients and their living donors, may be inconsistent.

DEMOGRAPHICS OF THE END-STAGE RENAL DISEASE POPULATION

United States

Each year, the United States Renal Data System (USRDS) provides updated demographic information about patients with kidney disease who are treated either with dialysis or renal transplantation in the United States. Excerpts of this massive report, presented in an easily accessible fashion, are published annually in the January issue of the *American Journal of Kidney Diseases* (see "Selected Readings"). According to the 2008 report, as of December 2006, about 400,000 patients were receiving maintenance dialysis in the United States (Table 1.2 and Fig. 1.1) and about 150,000 had a functioning transplant. The increase in number of dialysis patients has slowed somewhat, and this number now increases at an annual rate of about 4%. By the year 2010, the number of dialysis patients is expected to approach 500,000. About 7% of the Medicare population suffers from CKD.

About 40% of patients receiving regular dialysis are older than 65 years, and the mean age of those beginning treatment is greater than 60 years; these numbers are projected to increase in the next decade. This phenomenon has been described as the "gerontologizing" of nephrology, and accounts for the frequency of aged of patients being evaluated for, awaiting, and undergoing renal transplantation (see Chapters 7 and 10). In the ESRD population, men slightly outnumber women, and more than 30% are African American. The prevalence of African Americans in the ESRD population thus exceeds by threefold their percentage in the general population of the United States. Much evidence also links poverty to CKD, either as a direct impact of poverty on CKD or indirectly through the increased health care burden linked to poverty-associated diabetes and hypertension. The poor and socially deprived have a greater prevalence of ESRD. Access to renal care, dialysis, and transplantation may also be affected by social deprivation. Poverty and social deprivation are emerging as major risk markers for CKD in both developing and developed countries.

Despite improvements in the clinical management of both diabetes mellitus and

hypertension, these two diagnostic categories remain by far the most common causes of ESRD. In Hispanic and Native American patients, the burden of diabetes is particularly heavy. Older patients and those with diabetes are more likely to be accepted for dialysis in the United States than in other countries. Moreover, patients now beginning dialysis in the United States have more comorbid medical conditions than those accepted for treatment in the 1980s. Congestive heart failure is present in 35% of the incident dialysis population, whereas coronary artery disease can be found in up to 40% of the incident dialysis population in some published reports.

There has been a steady increase the number of deceased donor kidney transplants performed each year: about 8500 in 2002 and 10,500 in 2008. This increase largely reflects the efforts of the Organ Donation and Transplantation Breakthrough Collaborative (see Chapter 4). The annual number of living donor

transplants has fallen somewhat to about 6000 in 2008 despite an increase in the number of transplants from living donors who are not biologically related to the recipient (see Chapter 6). The number of patients who are awaiting deceased donor renal transplantation is progressively rising (Fig. 1.1), reaching more than 80,000 by early 2009. About one third of these patients have been designated "inactive," and the "active" transplant waiting list has remained stable (see Chapter 4). There are likely many ESRD patients who are potential transplant candidates but have not been referred to transplant programs, so there remains a massive gap between the supply of and the demand for deceased donor kidneys. Consequently, the average waiting time for a deceased donor transplant has increased substantially, and it is now measured in years for most patients (see Chapters 4 and 7). The increasing incidence of CKD and ESRD, in a background of a national "epidemic" of obesity, diabetes, and inadequately treated hypertension, makes it unlikely that waiting time for a transplant will be eradicated in the absence of more effective CKD prevention. Demographics of the Dialysis Population in the United States*

TABLE 1.2 Demographics of the Dialysis Population in the United States*

Demographic Age (yr)	Percentage
<20	0.7

20-44	15
45-64	41
65-74	22
>75	21
Sex	
Male	54
Female	46
Race	
African American	37
White	55
Asian	4

Native American	2
Primary ESRD Diagnosis	
Diabetic nephropathy	43
Hypertension	28
Glomerulonephritis	11
Cystic kidney disease	3
Urologic disease	2
Other[†]	13

[*]Point prevalence as of December 31, 2006.

[†] Nearly 10% of patients with end-stage renal disease (ESRD) have a failed transplant.

From Collins AJ, Foley RN, Herzog C, et al: Excerpts from the United States

Renal Data System 2008 Annual Data Report. Am J Kidney Dis 2009;53(Suppl 1):S1—S374, with permission.

Worldwide

The worldwide dialysis population is estimated to be greater than 1 million persons. The highest prevalence and incidence rates for ESRD are reported from Taiwan, Japan, and the United States. The high rate in the United States (Fig. 1.2) reflects, in part, the high incidence of ESRD in African Americans.

Other factors, particularly limitations on the availability of dialysis, also play a role. Age is an important factor for patient selection in some countries, whereas in the United States, there is no age restriction for providing dialysis, and this largely explains the steady rise in the average age of the U.S. dialysis population. Modalities for the management of ESRD vary among countries. For example, in the United Kingdom, Australia, and Canada, home dialysis is used extensively, whereas this therapeutic approach is uncommon in Japan and the United States. Renal transplantation rates from both deceased and living donors vary considerably among developed countries (Fig. 1.3). Legal constraints and cultural barriers to the acceptance of brain-death criteria or living donation are important determinants of national transplantation rates.

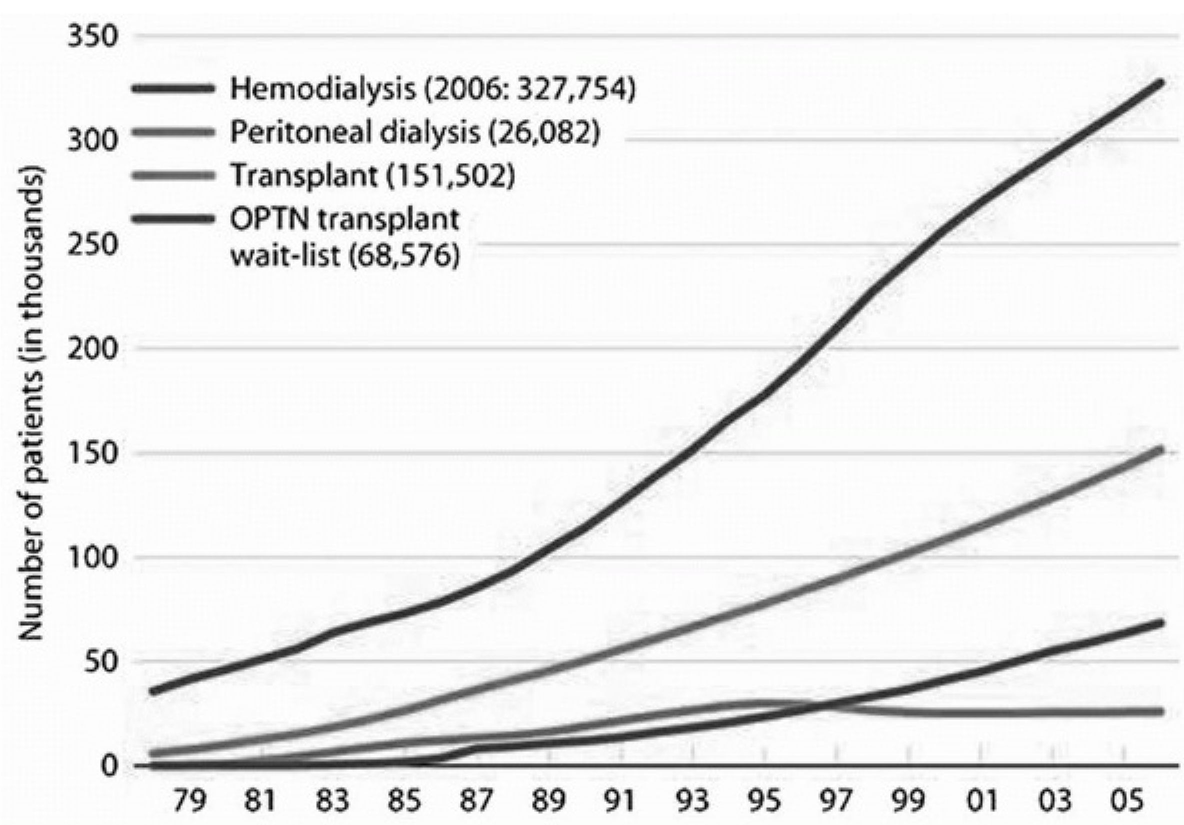


FIGURE 1.1 2008 USRDS Annual Data Report. Prevalent patient counts by modality.

TREATMENT OPTIONS FOR END-STAGE RENAL DISEASE: DIALYSIS

Hemodialysis

Hemodialysis is the predominant technique for treating ESRD throughout the world. In the United States, most patients start their ESRD care with hemodialysis. The procedure can be done either in a medical facility specifically designed for this purpose or in the patient's home. When performed in a dialysis facility, hemodialysis treatments typically range in length from 2.5 to 5 hours, and they are usually done 3 times a week. For highly motivated patients with a suitable living environment and a willing assistant, usually a spouse, hemodialysis can be done at home, freeing the patient from the need to visit a dialysis center and to adhere to a rigid treatment schedule.

During dialysis, solutes are removed by diffusion across a semipermeable membrane within a dialyzer, or artificial kidney, from blood circulated through an extracorporeal circuit. Fluid retained during the interval between treatments is removed by regulating the hydrostatic pressure across the membrane of the dialyzer. Most hemodialysis machines now control fluid removal, or ultrafiltration, using volumetric systems controlled by electronic microcircuits to ensure accurate and predictable results.

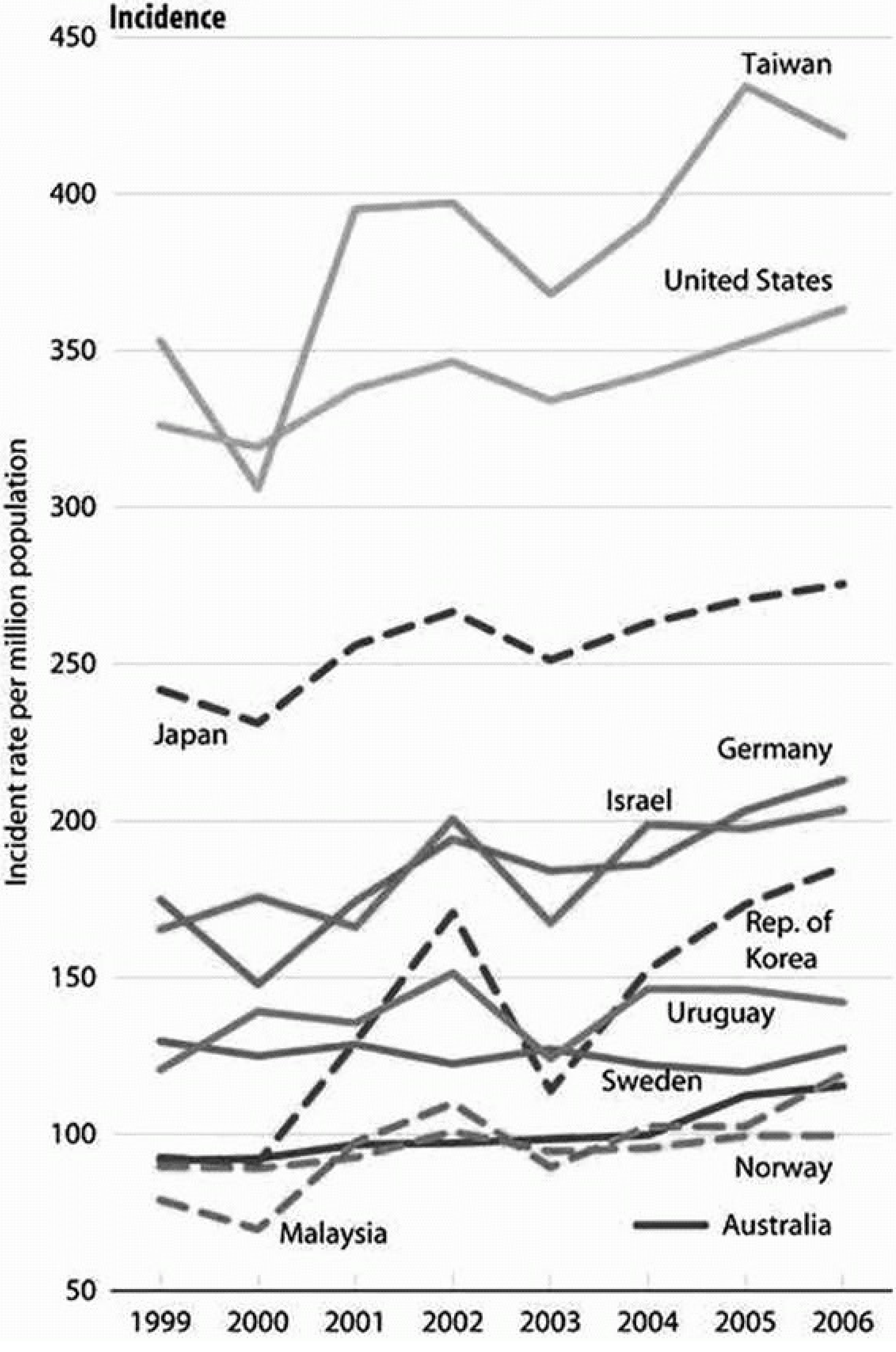


FIGURE 1.2 2008 USRDS Annual Data Report. Comparison of end-stage renal disease (ESRD) incidence worldwide.

Hemodialysis is generally well tolerated, although ultrafiltration can cause hypotension, nausea, and muscle cramps. Older patients and those with established CVD

may tolerate the procedure less well. Vascular access failure from repeated cannulation procedures and the need for intermittent heparinization to prevent clotting in the extracorporeal blood circuit are additional concerns, particularly in diabetic patients. The intermittent nature of hemodialysis, which results in rapid changes in extracellular fluid volume, blood solute concentrations, and plasma osmolality, may contribute to fatigue and malaise after treatment. This reality has led to attempts to increase the frequency and thus

overall solute and fluid removal capabilities of hemodialysis. Increasing the number of treatments to five or six per week, increasing the time per treatment, and using daily nocturnal dialysis are approaches currently under intense study. These approaches are generally performed at home because they are not easily accommodated in the schedule of a dialysis center. Most dialysis membranes are now synthetic and provide a reasonably efficient removal of low-molecular-weight solutes.

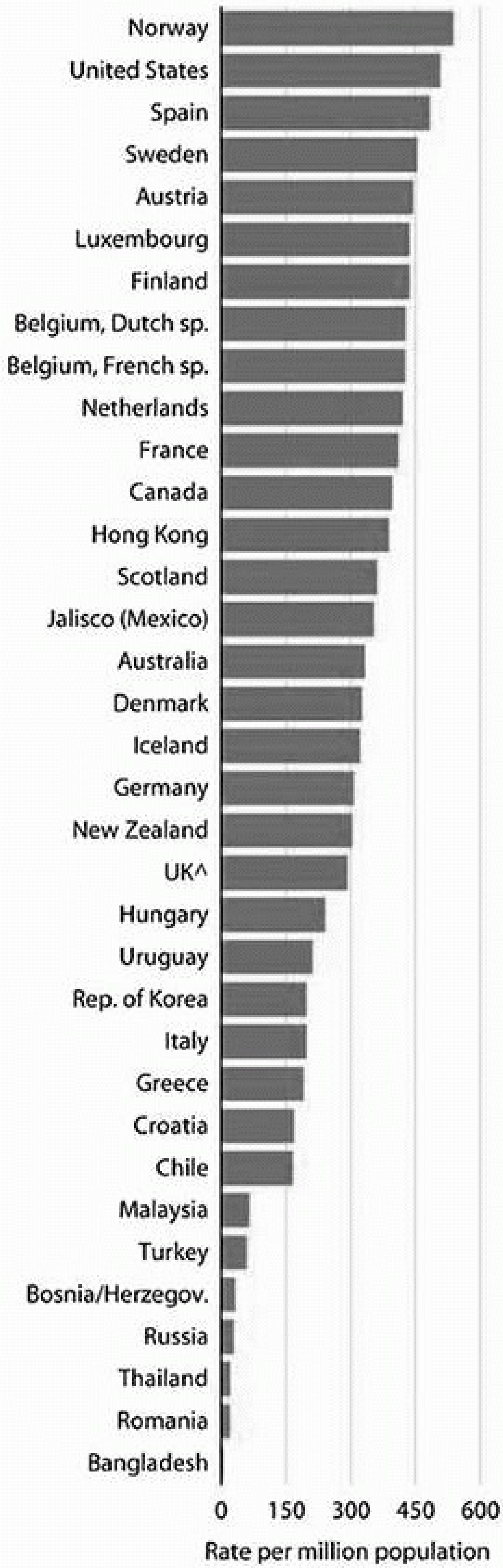


FIGURE 1.3 2008 USRDS Annual Data Report. Prevalent rates of functioning grafts in selected countries, 2006.

Urea clearances of 180 to 200 mL per minute are readily achieved during hemodialysis.

Despite the favorable water permeability of synthetic membranes, the clearance of middle- and higher-molecular-weight toxins remains a fraction of that achieved for small substances. Although the minute-by-minute removal of low-molecular-weight solutes during hemodialysis may actually exceed that provided by normal endogenous renal function, the intermittent nature of hemodialysis as employed in clinical practice substantially undermines the overall efficiency of this form of renal replacement therapy. Even for patients receiving 12 to 15 hours of hemodialysis per week, adequate solute clearance is provided for less than 10% of a 168-hour week. During the remaining 153 to 156 hours of each week, no additional solute removal is achieved unless there is some residual endogenous renal function. This residual function needs to be considered when recommending native kidney nephrectomy before transplantation (see Chapter 7).

Guidelines for implementing and monitoring dialysis prescriptions in the United States have increasingly recognized the critical role of cumulative weekly procedure length as a key element for maintaining hemodialysis adequacy. The amount of dialysis achieved can be measured objectively by the term Kt/V, where *K* represents the rate of urea clearance by the dialyzer; *t* represents the duration, in minutes, of the treatment session; and *V* represents the volume of distribution for urea. Longer dialysis sessions and more frequent treatments have been reported to provide better blood pressure, extracellular volume, and metabolic control in patients with kidney failure. *Such findings suggest that more dialysis is better than less dialysis*. More dialysis reduces the substantial disparity between the amount of solute removal provided by the standard thrice-weekly hemodialysis schedule and that achieved by normal endogenous renal function. The impact of alternative dialysis regimens on long-term clinical outcomes is not yet known. Readers are referred to the K/DOQI guidelines, published and updated by the National Kidney Foundation, which are an invaluable resource for the management of patients with ESRD.

The hemodialysis procedure requires access to the patient's circulation to provide continuous blood flow to the extracorporeal dialysis circuit. For ongoing hemodialysis therapy, an autologous arteriovenous (A-V) fistula is the most reliable type of vascular access and the one associated with the best prognosis. Long-term patency is greatest with A-V fistulas, and the incidence rates of thrombosis and infection are low. A-V grafts that use synthetic materials are often placed in elderly patients and in diabetic patients whose native blood vessels may be inadequate for the creation of a functional A-V fistula. Complication rates are considerably higher, however, with grafts than with fistulas. Thrombosis is a recurrent problem, and it frequently occurs because of stenosis at the venous end of the graft, where it forms an anastomosis with the native vein. Infections and the formation of pseudoaneurysms are more common with grafts than with fistulas. Temporary venous dialysis catheters are used to establish vascular access when hemodialysis must be started urgently. Other venous catheters, designed to be used over longer intervals, are frequently used as a method for providing vascular access for patients undergoing regular

hemodialysis, particularly when treatment is first begun or when permanent access sites require surgical revision. Reliance on these approaches should be limited, however, and permanent access should be established using A-V fistulas or A-V grafts as soon as ESRD is deemed inevitable.

Stenotic lesions in large proximal veins in the thorax are an increasingly recognized complication of indwelling venous dialysis access catheters. These may involve the subclavian and innominate veins and the superior vena cava. Their presence can interfere with successful placement of permanent vascular access by producing venous hypertension that interferes with venous blood return from A-V fistulas or grafts. The sustained use of venous dialysis access catheters should be avoided. Early referral of patients with CKD to nephrologic care and elective placement of dialysis access, preferably in the form of an arterial autologous fistula, reduces morbidity. This becomes particularly important for patients who do not have a living kidney donor and who thus are likely to experience a prolonged wait on the deceased donor transplant waiting list (see Chapter 7). As a rule, a fistula should be placed at least 6 months before the anticipated start of hemodialysis treatments.

Peritoneal Dialysis

Peritoneal dialysis is an alternative to hemodialysis that exploits the fluid and solute transport characteristics of the peritoneum as an endogenous dialysis membrane. In the United States, less than 10% of patients start dialysis with this technique. In many countries, peritoneal dialysis is more popular. Peritoneal dialysis can be done either as *continuous ambulatory peritoneal dialysis* (CAPD) or as *continuous cycling peritoneal dialysis* (CCPD). Access to the peritoneal cavity is achieved by surgically placing a silastic catheter (often called a Tenckhoff catheter) of varying design through the abdominal wall. Surgery is done several weeks before starting treatment, and patients are trained subsequently to perform their own dialysis procedures.

Peritoneal dialysis is accomplished by instilling a specified volume of peritoneal dialysis fluid, typically between 1500 and 3000 mL, into the abdominal cavity by gravity-induced flow, allowing the fluid to remain in the abdomen for a defined period, and then draining and discarding it. During each dwell period, both solute removal and ultrafiltration are achieved. Solute removal occurs by diffusion down a concentration gradient from the extracellular fluid into peritoneal dialysate, with the peritoneal membrane acting as a functional semipermeable dialysis membrane. The efficiency of removal of small solutes is relatively low compared with hemodialysis, whereas the clearance of higher-molecular-weight solutes is somewhat better. Ultrafiltration is accomplished by osmotic water movement from the extracellular fluid compartment into hypertonic peritoneal dialysate that contains a high concentration of dextrose, ranging from 1.50 to 4.25 gram percent. The lower rates of solute removal that characterize peritoneal dialysis are offset by prolonged treatment times. For CCPD, an

automated cycling device is used to regulate and monitor the dialysate flow into and out of the abdominal cavity.

Four to 10 dialysis exchanges, ranging from 1 to 3 L each, are done nightly over 8 to 10 hours. A variable amount of dialysate is left in the abdomen during the day to provide additional solute and fluid removal. For CAPD, dialysis is done 24 hours a day, 7 days a week, using manual exchanges of peritoneal dial-ysate 4 or 5 times per day. Peritoneal dialysis has certain advantages over hemodialysis, including the maintenance of relatively constant blood or serum levels of urea nitrogen, creatinine, sodium, and potassium. Hematocrit levels are often higher than for patients receiving hemodialysis, and gradual and continuous ultrafiltration may provide better blood pressure control. Because it is

a form of self-care, peritoneal dialysis promotes patient independence. The major complication of peritoneal dialysis is bacterial peritonitis. Its frequency varies considerably among patients and among treatment facilities, but it occurs with an average frequency of one episode per patient per year. When bacterial peritonitis is diagnosed promptly and treatment is begun immediately, infections are generally not severe and resolve within a few days with appropriate antibiotic therapy. Episodes of peritonitis are an ongoing threat, however, to the long-term success of peritoneal dialysis, and they can lead to scarring of the peritoneal cavity and to the loss of the peritoneum as an effective dialysis membrane. In the past, gram-positive organisms, such as *Staphylococcus epider-midis* or *Staphylococcus aureus,* accounted for most cases of peritonitis, but almost half of episodes are now caused by gram-negative bacteria. Fungal peritonitis typically causes extensive intra-abdominal scarring and fibrosis, and it often leads to the failure of peritoneal dialysis as an effective mode of treatment.

TABLE 1.3 Comparison of Hemodialysis and Peritoneal Dialysis

Advantages	**Disadvantages**
Hemodialysis	
Short treatment time	Need for heparin

Highly efficient for small solute removal	Need for vascular access
	Hypotension with fluid removal
Socialization occurs in the dialysis center	Poor blood pressure control
	Need to follow diet and treatment schedule
Peritoneal Dialysis	
Steady-state chemistries	Peritonitis
Higher hematocrit	Obesity
Better blood pressure control	Hypertriglyceridemia
Dialysate source of nutrition	Malnutrition
Intraperitoneal insulin administration	Hernia formation
Self-care form of therapy	Back pain

Highly efficient for large solute removal	
Liberalization of diet	

With few exceptions, hemodialysis has no medical advantage over peritoneal dialysis. Both effectively manage the consequence of uremia (Table 1.3). Matters of individual lifestyle and other psychosocial issues should be considered when selecting a particular mode of dialysis. Home hemodialysis provides an opportunity for independence and rehabilitation, but it can be a cause of substantial emotional stress for the dialysis assistant and other family members. In some home settings, neither hemodialysis nor peritoneal dialysis is advisable. In-center hemodialysis can provide ongoing social interaction for older, single patients who have few friends or family members available to provide support.

Long-Term Complications of Dialysis

As survival for patients on regular dialysis improves, a number of debilitating complications of either long-term renal failure or protracted dialysis may develop, even in well-rehabilitated and medically adherent patients. As the waiting time for deceased donor renal transplants inexorably increases (see Chapter 4 and Fig. 1.1), these complications are more likely to manifest clinically. Their presence may affect the medical indications for transplantation, and they may influence the choice of renal transplantation as a therapeutic option (see Chapter 7). The longer patients receive dialysis, the greater the risk for post-transplantation morbidity, mortality, and graft loss (see Chapter 6 and Fig. 1.4). The following discussion concentrates on those long-term complications that are most relevant to the posttransplant course.

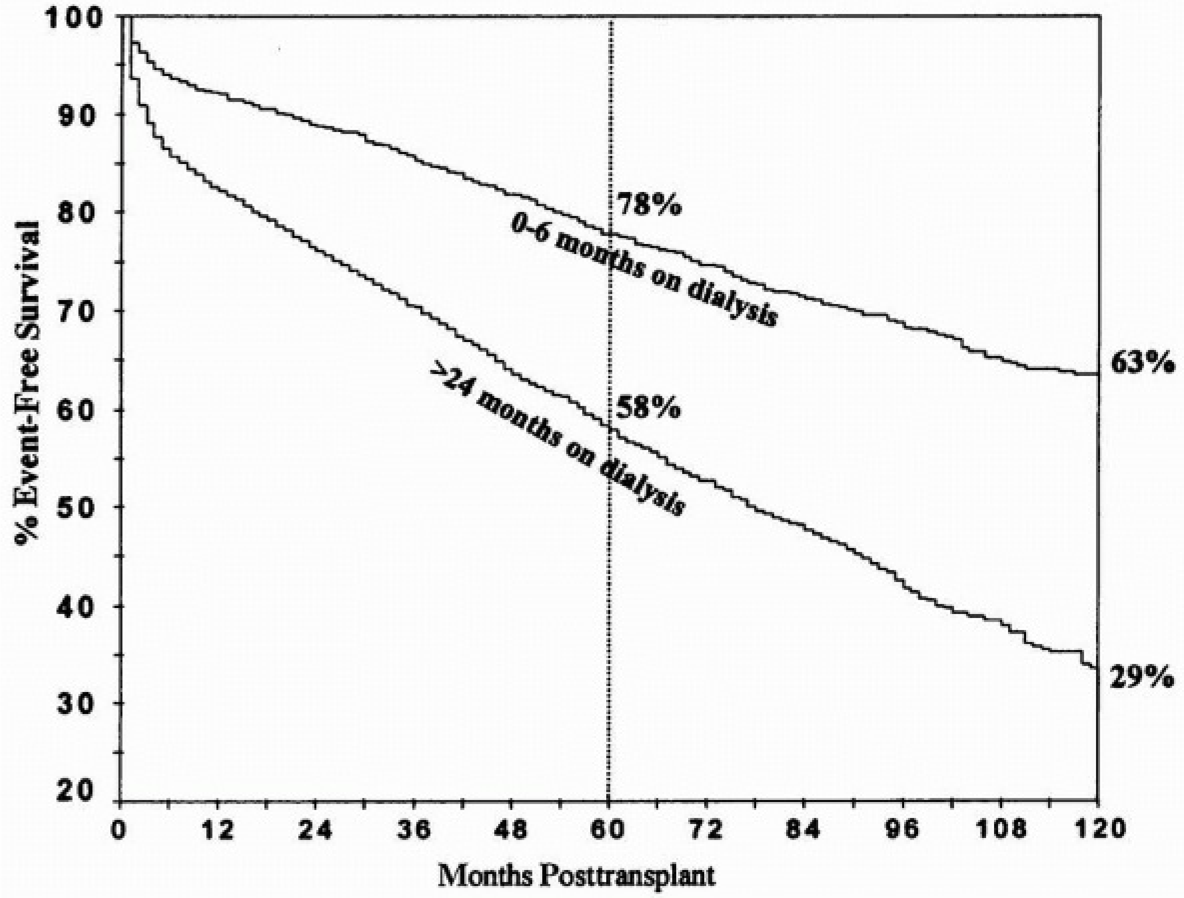


FIGURE 1.4 Unadjusted graft survival in 2405 recipients of paired kidneys with short compared with long end-stage renal disease time. (From Meier-Kriesche HU, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. Transplantation 2002;74:1377, with permission.)

Vascular Disease

The incidence of CVD in the CKD population has been described as reaching epidemic proportions. Even in the early stages of CKD, factors that contribute to the excess risk for CVD can be identified. Nearly all patients at some time during their clinical course develop hypertension, and many require multiple antihypertensive medications. The incidence of hypertension and diabetes as primary causes of CKD is increasing more rapidly than that of other diagnoses. Both traditional and novel risk factors account for the high incidence of CVD that is deemed responsible for close to 50% of all dialysis deaths.

Patients with kidney disease have a greater risk for developing left ventricular hypertrophy (LVH) than those in the general population, even in the early stages of CKD. The prevalence of LVH varies directly with the degree of renal dysfunction. At the time that regular dialysis is begun, 50% to 80% of patients have LVH, and the prevalence of coronary artery disease may reach 40%. Patients receiving regular dialysis have an

adjusted death rate from all causes that is estimated to be 3.5 times higher than that in the general population,

---

and the overall first-year mortality rate of hemodialysis patients in the United States is more than 20%. CVD accounts for 50% of this mortality at a rate that is 10 to 20 times greater than in the general population. Hypertensive patients have worse outcomes after dialysis, and patients with LVH have a twofold to threefold higher death rate from cardiac causes.

Progressive calcification of the coronary arteries occurs over the years spent on dialysis and can be recognized even in young adult dialysis patients. Soft tissue calcification may also affect heart valves and the pelvic and peripheral vasculature. Vascular calcification is recognized increasingly as a complication of long-term dialysis. Mortality rates after myocardial infarction in dialysis patients are substantially higher than in the general population, a finding that probably reflects the severity of underlying CVD. The passage of time in patients receiving regular dialysis reflects ongoing exposure to multiple cardiovascular risk factors, and worsening myocardial function has been described, particularly during the first year of treatment. Although much attention is given to the cardiac manifestation of vascular disease, 10% of dialysis patients have peripheral vascular disease and 15% cerebrovascular disease. All these observations may explain the consistent finding that post-transplantation prognosis worsens the longer patients are treated with dialysis before renal transplantation (Fig. 1.4).

Anemia

The routine administration of recombinant erythropoietin (epoetin alfa) to treat the anemia of CKD and ESRD has had an enormously beneficial impact on morbidity. Fatigue, depression, cognitive impairment, sexual dysfunction, and LVH all improve with adequate treatment of anemia. The degree to which anemia is corrected is, to a large extent, determined in the United States by Medicare reimbursement policies that govern the target level of hemoglobin. Readers are referred to the K/DOQI anemia guidelines for updated recommendations. Successful treatment of anemia in dialysis patients is closely linked to replenishment of iron stores. Darbepoetin alfa (Aranesp) is a protein that stimulates erythropoiesis and is closely related to erythropoietin. Because its terminal half-life is about threefold longer than that of epoetin alfa, darbepoetin alfa can be administered less frequently.

Renal Osteodystrophy

Secondary hyperparathyroidism and high-turnover bone disease often develop in patients with ESRD. Several factors contribute to excess parathyroid hormone (PTH) secretion in patients with renal failure. These factors include hypocalcemia, diminished renal calcitriol production, skeletal resistance to the calcemic actions of PTH,

alterations in the regulation of *pre-pro-PTH* gene transcription, reduced expression of receptors for vitamin D and calcium in the parathyroid glands, and hyperphosphatemia caused by diminished renal phosphorus excretion. Progressive parathyroid gland hyperplasia occurs often. Severely affected patients experience bone pain, skeletal fracture, and substantial disability. Hypercalcemia and soft tissue and vascular calcifications may develop. Treatment with one of several vitamin D sterols may lower plasma PTH levels and restore bone formation and bone-remodeling rates toward normal. Episodes of hypercalcemia and hyperphosphatemia occur frequently, however, during vitamin D therapy. Newer therapeutic agents, such as calcimimetic compounds, may offer an alternative for controlling excess PTH secretion in patients undergoing dialysis without aggravating disturbances in calcium and phosphorus metabolism.

Low-turnover lesions of renal osteodystrophy include osteomalacia and adynamic bone. In the past, osteomalacia was found in patients with tissue aluminum accumulation, but aluminum-related bone disease is now uncommon.

Most ESRD patients with osteomalacia have evidence of vitamin D deficiency, mineral deficiency, or both. The adynamic lesion of renal osteodystrophy occurs in patients with normal or only modestly elevated serum PTH levels. It can also be a manifestation of aluminum toxicity, and affected patients have severe bone pain, muscle weakness, and fractures. Adults with adynamic bone may be at increased risk for vertebral fracture. The impact of transplantation on uremic bone disease is discussed in Chapter 10.

Uremic Neuropathy

Peripheral neuropathy is a feature of chronic renal failure, and encephalopathy will develop if appropriate renal replacement therapy is not begun. A mild stable sensory neuropathy is common even in nondiabetic dialysis patients; it is usually largely sensory and detected clinically by impaired vibration and position sense. It may be a source of pain and “restless legs.” Neuropathy can recover dramatically after successful transplantation. It may also improve substantially after intensification of dialysis treatment.

Severe encephalopathy is rare in patients who receive adequate amounts of dialysis. Impairments in the ability to concentrate and minor memory loss represent more subtle manifestations of cognitive impairment in dialysis patients, and improvement after transplantation is gratifying. Autonomic neuropathy in nondiabetic patients receiving dialysis can be recognized by impaired heart rate variability, and it may account for variations in blood pressure during dialysis procedures. Autonomic dysfunction is also reversible after renal transplantation. Neuropathy contributes to sexual dysfunction in many dialysis patients. About half of men suffer from erectile dysfunction; menstrual disturbances and infertility are common in women. Improvement after transplantation is variable and is discussed in Chapter 10.

Acquired Cystic Disease and Cancer of the Kidney and Urinary Tract

Patients on all forms of maintenance dialysis are at increased risk for cancer, especially of the kidney and urinary tract. The risk increases with time. Kidney cancer rates are elevated nearly fourfold. The pattern of risk is consistent with causation through acquired cystic disease. Urothelial cancer risk is increased by about 50%, presumably as a result of the carcinogenic effects of certain primary renal diseases. The incidence of acquired cystic disease rises progressively with increasing duration of CKD and time on dialysis. The incidence of multiple cysts has been reported to be 7% in those with chronic renal failure and 22% in those on maintenance dialysis. The condition is characterized by multiple, usually bilateral, renal cysts in small, contracted kidneys and is, therefore, easily distinguishable from adult polycystic kidney disease. Cysts may become infected, bleed, or cause localized pain, and they can undergo malignant transformation. Suspicious cysts should be imaged at regular intervals, and concern about malignant transformation may be an indication for pretransplantation nephrectomy. The capacity for malignant transformation should not be forgotten in the post-transplantation period.

Dialysis Access Failure

Early referral before the initiation of regular hemodialysis is required and is essential for establishing optimal long-term vascular access. For patients managed with hemodialysis, reliable vascular access is a life-sustaining aspect of medical care. Vascular access failure not only threatens the near-term well-being of patients but also has long-term implications with regard to the success of ongoing renal replacement therapy. Access-related morbidity accounts for almost 25% of all hospital stays for ESRD patients and for close to 20% of the

---

cost of ESRD care. As discussed previously, A-V fistulas are the gold standard for long-term vascular access for hemodialysis. A-V grafts almost invariably undergo thrombosis; their 3-year cumulative patency rate has been estimated to be about 50%. Because the number of sites that can be used for permanent vascular access placement is limited, the choice of A-V grafts for long-term vascular access conveys the risk for ultimately losing all remaining vascular access sites, rendering further hemodialysis technically impossible.

TREATMENT OPTIONS FOR END-STAGE RENAL DISEASE: TRANSPLANTATION

The relative prevalence of the major ESRD treatment options between 1979 and 2005 in the United States is shown in Fig. 1.1.

Deceased donor transplantation accounts for about half of all kidney transplantations in

the United States, the remainder being from living donors. The rate of renal transplantation varies considerably among patient groups. Transplantation rates are lower in older patients, who represent a relatively high-risk group (see Chapter 7). Transplantation rates have tended to be lower in African American ESRD patients, partly for reasons that constrain access to deceased donor organs (see Chapter 3). Patient and graft survival rates in the United States are shown graphically in Figure 1.5. Mean 1-year graft survival for all types of living donor transplants is about 95% (Fig. 3.3). In many centers, it is greater than 90% for all match grades of deceased donor transplants.

Patient Survival

Difficulties with Data Analysis

To help select the most appropriate therapeutic option for patients with advanced CKD, clinicians and patients are understandably interested in comparative survival rates among various treatment modalities. Such comparisons are difficult, however, because data in the literature often do not reflect the fact that patients change treatment modalities frequently and that the characteristics of patients selected for each modality may differ substantially when therapy is begun. For dialysis patients, a number of comorbid factors can adversely affect survival; these include increased age, diabetes, coronary artery disease, peripheral vascular disease, chronic obstructive pulmonary disease, and cancer. Overall, African Americans have a better survival rate on dialysis than do non-African Americans, as do obese patients, whereas certain renal diagnoses, such as amyloidosis, multiple myeloma, and renal cell cancer, are associated with poorer prognoses. Poor nutritional status, as measured by serum albumin and prealbumin levels, has been increasingly recognized as an important predictor of survival during long-term dialysis (see Chapter 19). Exclusion of consideration of these factors limits the accuracy of comparisons among therapeutic modalities. The concept of *reversed epidemiology* describes the phenomenon whereby factors associated with a poor prognosis in individuals free of renal disease (e.g., obesity, hyperlipidemia, hypertension) may be associated with an improved prognosis in dialysis patients.

Comparison of Treatment Modalities

Most of the data comparing survival rates for patients treated with hemodialysis, CAPD, and deceased donor kidney transplantation suggest that an individual's state of health before treatment, rather than the treatment modality itself, is the most important factor in determining survival. Healthier dialysis patients are more likely to be placed on the waiting list for transplantation. The annual

---

mortality rate for dialysis patients awaiting a transplant is about 6%, a value that is several-fold lower than the overall mortality rate among all dialysis patients.

Waitlisted dialysis patients enjoy a further reduction in the relative risk for death if they subsequently receive a transplant rather than continue to receive dialysis. This phenomenon is illustrated graphically in Figure 1.6, which records the relative risk for death for dialysis patients who were placed on a deceased donor transplant waiting list. The long-term survival rates were better for transplant recipients who received either an “ideal” or “marginal” donor kidney (see Chapter 4). This survival benefit can be recognized within the first post-transplantation year despite the higher mortality rates associated with the surgical procedure and with immunosuppressive therapy. The magnitude of the survival benefit varies according to the quality of the transplanted kidney and the patient characteristics at the time of placement on the waiting list. It is most marked for young diabetic patients. As a gross approximation, it can be said that a high-quality donor kidney has the capacity to about double the anticipated life span of a waitlisted dialysis patient.

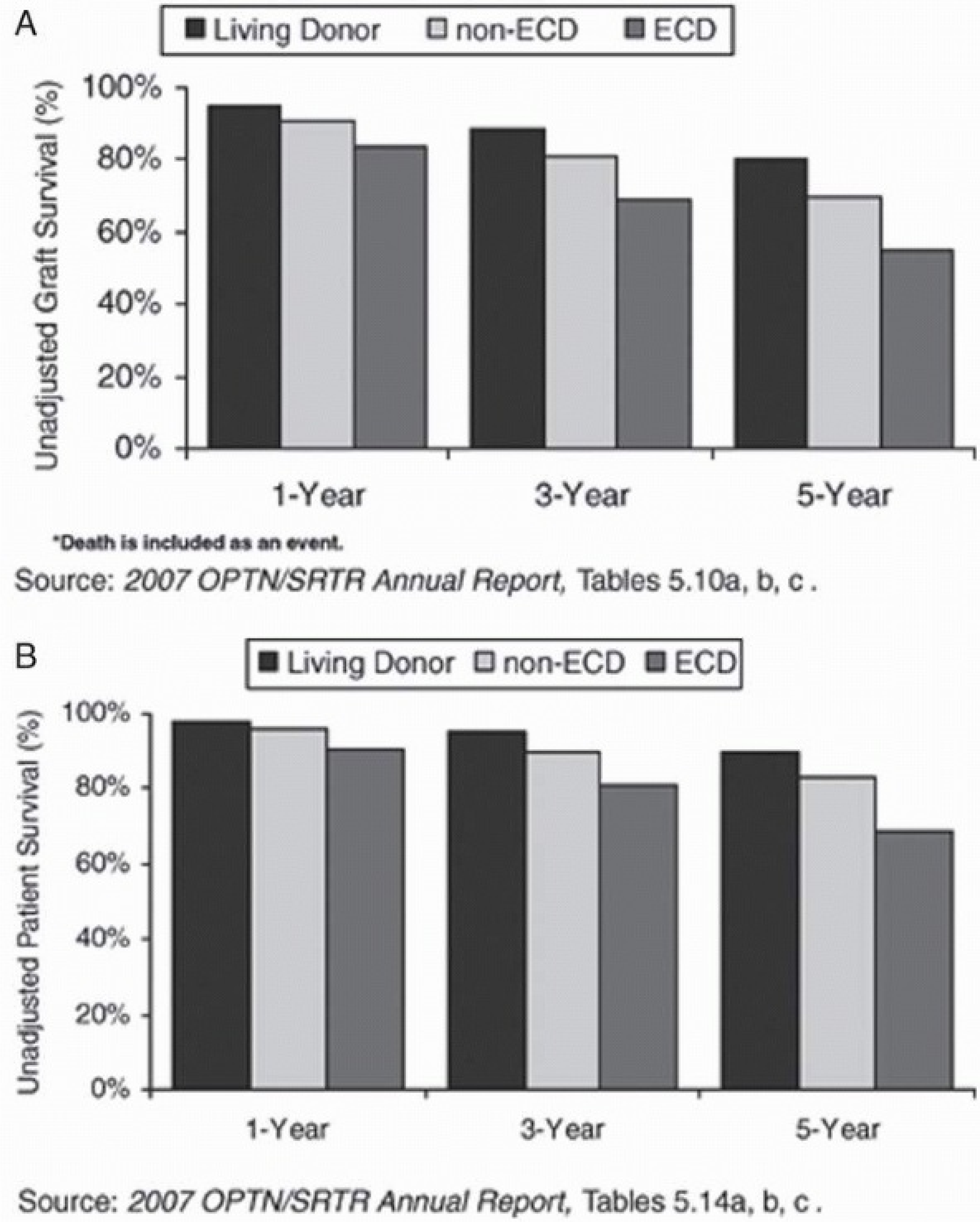


FIGURE 1.5 A: Unadjusted 1-year, 3-year, and 5-year kidney graft survival times (*), by donor type: 2000 to 2005. **B:** Unadjusted 1-year, 3-year, and 5-year kidney recipient survival times, by donor type: 2000 to 2005. (From Leichtman A, Cohen D, Keith D, et al. Kidney and pancreas transplantation in the United States 1997-2006: the HRSA breakthrough collaborative and the 58 DSA challenge. Am J Transplant 2008;8:946-957, with permission.) ECD, extended criteria donor (see Chapter 4).

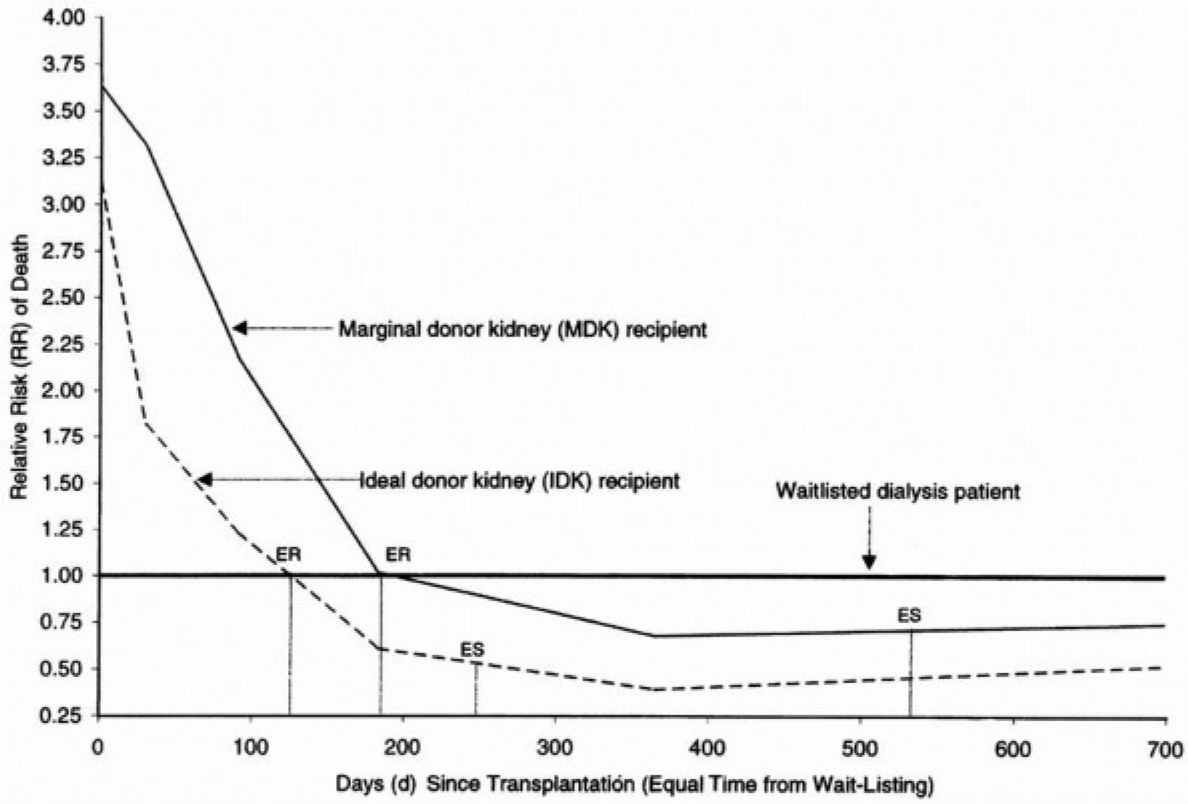


FIGURE 1.6 Survival benefit of transplantation versus remaining on the waiting list for recipients of "ideal" (*interrupted line*) and "marginal" (*solid line*) kidneys. Note that in the early period after transplantation, the risk for death is higher for transplant recipients than for waitlisted patients. Within a short period, somewhat longer for recipients of marginal kidneys, the risk for death (*ER*) and chance of survival (*ES*) equalize. Thereafter, transplantation has a persistent survival benefit. (From Ojo AO, Hanson JA, Meier-Kriesche H, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and waitlisted transplant candidates. J Am Soc Nephrol 2001;12:589, with permission.)

Cost of Therapy

The annual cost of medical care for patients undergoing chronic hemodialysis in the United States is about $75,000. Medical costs during the first year after renal transplantation are considerably higher and are estimated to be nearly $100,000. The cost of care is less, however, after the first post-transplantation year when compared with the cost of dialysis, despite the about $10,000 annual cost of immunosuppressive therapy (see Chapter 20). The mean cumulative costs of dialysis and transplantation are about the same for the first 4 years of therapy. Thereafter, overall costs are lower after successful renal transplantation.

Quality of Life

Most studies demonstrate that the quality of life (QOL) of patients receiving peritoneal dialysis exceeds that of patients receiving hemodialysis in a dialysis center. Home hemodialysis patients reportedly have a high QOL, although selection factors, such as the level of patient motivation and the patient's overall health status at the beginning of treatment, make it difficult to attribute this benefit to the modality alone. Most dialysis patients select renal transplantation with the hope of improving their QOL, and recipients of successful transplantations consistently report a better QOL than do patients undergoing either peritoneal dialysis or home hemodialysis. Life satisfaction, physical and emotional well-being, and the ability to return to work are all significantly better in transplant recipients than in dialysis patients. Transplantation often corrects or improves some complications of uremia that are typically not reversed fully by dialysis; these include anemia, peripheral neuropathy, autonomic neuropathy, and sexual dysfunction (see Chapter 10). The QOL for recipients of living donor transplants compares favorably to that seen in the general population. QOL surveys of dialysis and transplant patients suggest that, as a gross approximation, dialysis patient value a year of life on dialysis at 80% of a year of life with a functioning transplant.

INITIATION OF END-STAGE RENAL DISEASE THERAPY

An in-depth discussion of the indications for starting renal replacement therapy is beyond the scope of this text. Most patients with progressive renal failure develop symptoms of kidney failure and will require treatment for ESRD when the GFR falls to below 15 mL per minute or the serum creatinine level increases to more than 10 mg/dL. Many patients, particularly those with diabetes, develop symptoms at lower serum creatinine levels and at higher GFR values. Hemodialysis or peritoneal dialysis access should be arranged sufficiently far in advance so that treatment can be started when needed, rather than on an urgent or emergency basis. Patients can then be spared the suffering and risk that are inevitably associated with advanced CKD. Because permanent vascular access for hemodialysis requires 4 to 8 weeks to mature, placement should be undertaken early so that the use of temporary venous catheters for dialysis access can be avoided. For peritoneal dialysis, peritoneal catheter placement can be delayed until dialysis is more imminent because only 2 to 4 weeks is required before the access can be used. Early referral of CKD patients to the care of a nephrologist about doubles the chance of being placed on the waiting list and of receiving a transplant before the commencement of dialysis.

The decision to start dialysis is a clinical one, however, and should be based on the plasma levels of creatinine, urea nitrogen, and selected electrolytes as well as on a careful assessment of uremic symptoms. Outcomes after dialysis are better for patients who start early rather than late and who start electively rather than emergently. Predialysis or preemptive transplantation is discussed in Chapter 7. It is the preferred therapeutic modality for ESRD in terms of morbidity, mortality, and long-term graft survival, but only 6% of ESRD patients receive preemptive transplantation. The allocation algorithm in place as of early 2009 (see Chapter 4) allows patients who have

not yet started dialysis to accrue waiting-time points when their GFR is 20 mL per minute or less. The very long waiting time for deceased donor organs makes it unlikely, however, that a predialysis patient without a living donor will be allocated a kidney. Predialysis patients who are placed on the deceased donor transplant waiting list and those prepared for living donor transplantation should be warned explicitly not to delay establishing access for dialysis should it become

---

necessary before a donor organ is available. Such an approach avoids the need for an unduly hurried pre transplantation preparation that can be dangerous and emotionally stressful both for patients and caregivers.

Selected Readings

Abraham G. The challenges of renal replacement therapy in Asia. Nat Clin Pract Nephrol 2008;4:643.

Chavlitdhamrong D, Danovitch GM, Bunnapradist, et al. Is there reversal of reverse epidemiology in renal transplant recipients? Semin Dialysis 2007;20:544-548.

Collins AJ, Foley RN, Herzog C, et al: Excerpts from the United States Renal Data System 2008 Annual Data Report. Am J Kidney Dis 2009;53(Suppl 1):S1-S374.

DeLoach S, Mohler E. Peripheral arterial disease: a guide for nephrologists. Clin J Am Soc Nephrol 2007;2:839-846.

Hallan S, Coresh J, Astor B, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol 2006;17:2275-2284.

Herzog C. Can we prevent sudden cardiac death in dialysis patients? Clin J Am Soc Nephrol 2007;2:410-412.

Hossain M, Goyder E, Rigby M, et al. CKD and poverty: a growing global challenge. Am J Kidney Dis 2009;53:166-174.

K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations. 2006 Updates: hemodialysis adequacy, peritoneal dialysis adequacy, and vascular access. Am J Kidney Dis 2006;48(Suppl 1).

Khan S, Xue J, Kazmi W, et al. Does predialysis nephrology care influence patient

survival after initiation of dialysis? Kidney Int 2005;67:1038-1046.

Leichtman A, Cohen D, Keith D, et al. Kidney and pancreas transplantation in the United States 1997-2006: the HRSA breakthrough collaborative and the 58 DSA challenge. Am J Transplant 2008;8:946-957.

Levey A, Eckardt K, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089-2100.

Meguid El, Nahas A, Bello A. Chronic kidney disease: the global challenge. Lancet 2005; 365:331-340.

Mehrotra R, Agarwal R. End-stage renal disease and dialysis. NephSAP 7:374-441;2008

Snyder J, Foley R, Collins A, et al. Prevalence of CKD in the United States: a sensitivity analysis using the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis 2009;53:218-228.

Szczech L, Harmon W, Hostetter T, et al. World Kidney Day 2009: Problems and challenges in the emerging epidemic of kidney disease. J Am Soc Nephrol 2009;20:453-464.

Vella J, Danovitch G. Transplantation. NephSAP 2008;7:6-55.

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

2

Transplantation Immunobiology

Didier A. Mandelbrot

Mohamed H. Sayegh

The immune response to a transplanted graft can be divided into three phases: recognition of foreign antigens, activation of antigen-specific lymphocytes, and the effector phase of graft rejection. If the transplant is between genetically different individuals of the same species, it is referred to as an *allogeneic* graft, or allograft. This allograft stimulates an immune response (alloresponse), which is mediated by alloreactive lymphocytes. This chapter focuses on the immune response to allografts. However, grafts can also be *autologous* (from an individual back onto that same individual), *syngeneic* (between genetically identical individuals), or *xenogeneic* (between individuals of different species).

The principal function of the immune system is to defend against infections. Fundamental to this function is the capacity of the immune system to discriminate between self and nonself antigens. The system is highly evolved in its ability to defend against various microbial infections and normally does not react against itself—the tissues of the host. The immune response to allografts is one example of a response to nonself antigens. Because transplantation is an unlikely event in the life of any organism, it has long been surprising that the immune system retains such a powerful ability to recognize and reject transplanted allografts. The explanation can now be provided in considerable detail.

THE RECOGNITION OF ALLOGRAFTS

Genetics of Allograft Rejection

Studies of the acceptance and rejection of tissue grafts exchanged between inbred mice established the following four basic principles that govern graft rejection:

1. Grafts exchanged between members of one inbred strain (syngeneic grafts) will survive.

2. Grafts between animals of different inbred strains (allografts) will be rejected.

3. Grafts from a parent to an Fl offspring of two different strains will survive (because the Fl offspring recognizes the graft from the homozygous parent as "self").

4. Grafts from an Fl offspring to a parent will be rejected (because the parent recognizes the graft from the heterozygous Fl as "nonself").

These results led to the realization that graft rejection was controlled by genes whose inheritance followed simple mendelian rules. The genes that determine the rejection or acceptance of tissue grafts are present in a locus on chromosome 6 that was named the major histocompatibility complex (MHC) (Fig. 2.1A). The gene products are MHC antigens or molecules. In humans, syngeneic grafts are those between identical twins—they survive because donor and recipient have identical MHC molecules. When donors and recipients of grafts differ in their histocompatibility antigens, the allogeneic grafts are rejected, unless the recipient receives immunosuppression. Genes other than MHC play smaller roles in graft rejection and are called *minor histocompatibility genes*. MHC incompatibilities lead to more vigorous rejection than minor incompatibilities, and in general, the greater the differences in the MHC, the more rapid the rejection.

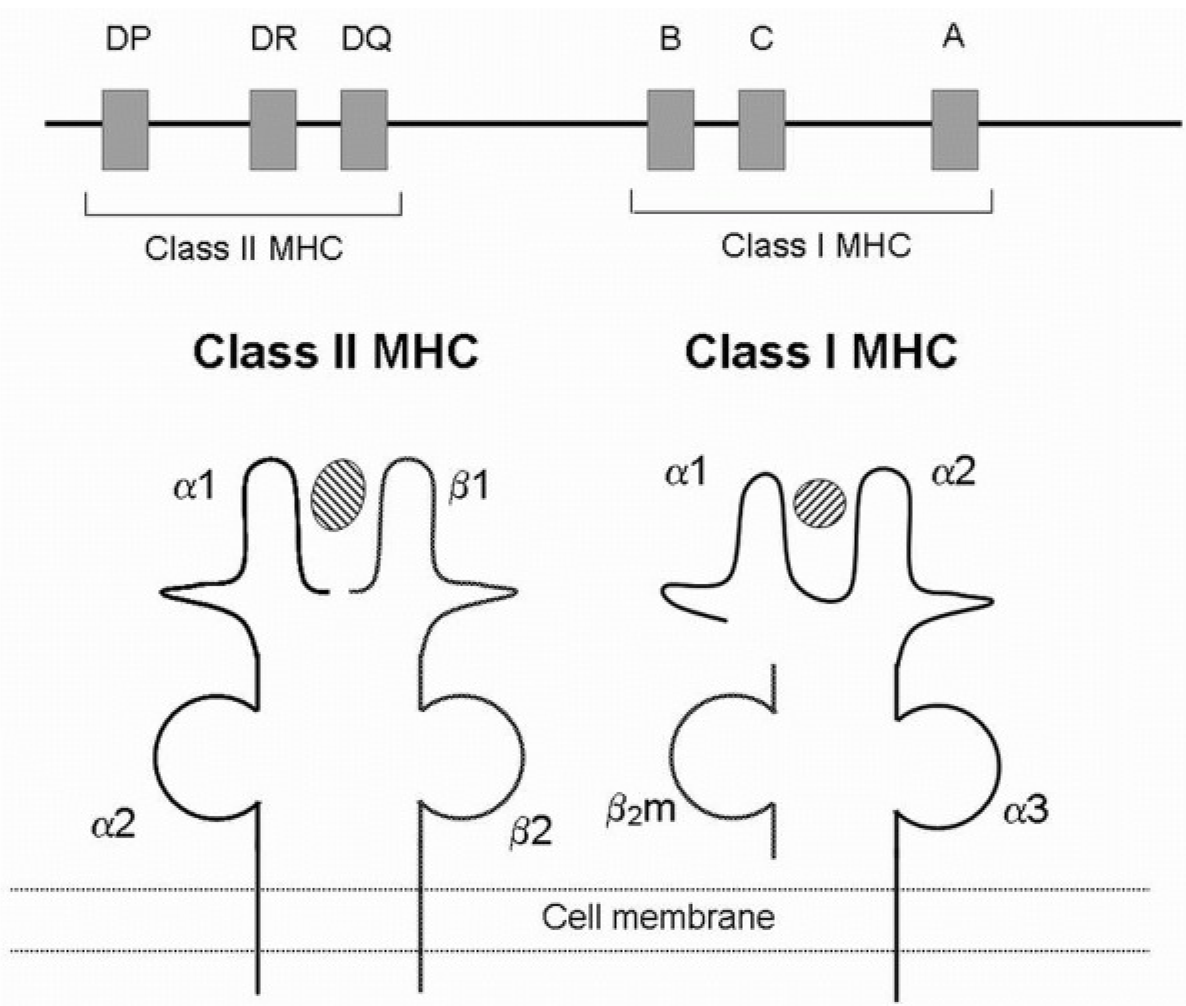


FIGURE 2.1 A: Schematic map of the human MHC genes found on chromosome 6. B:

Structure of MHC. The MHC class I molecule is composed of α polymorphic α chain noncovalently attached to a nonpolymorphic (β_2-microglobulin chain (β_2m). The α chain has three domains (α1, α2, and α3). The MHC class II molecule has a similar overall structure to class I, except that both α and β chains are polymorphic, and each has two domains (α1, α2 and β1, β2, respectively). Both class I and class II bind a peptide (cross-hatched) in their polymorphic region.

Major Histocompatibility Complex Molecules

The central event in the initiation of an alloresponse is the recognition of MHC/peptide complexes by a T-cell receptor. The MHC encodes a group of highly diverse cell surface proteins. Although these gene products were found in the 1940s to be the principal determinants of graft rejection, and thus named "histocompatibility" genes, their broader importance in controlling all immune responses to foreign antigens was only established in the 1960s. Many details of the structure and function of MHC molecules have since been established, and these are relevant to all responses to self and nonself antigens. Unlike antibody molecules, which can bind to essentially any class of molecule, including carbohydrates, lipids, and proteins, the antigen receptors of T cells primarily recognize peptides that are bound to MHC molecules. Consequently, T-cell activation is critically dependent on the MHC.

There are two types of MHC molecules: class I and class II molecules. In humans, the MHC genes are called human leukocyte antigen (HLA) genes and include the class I genes HLA-A, HLA-B, and HLA-C and the class II genes HLA-DP, HLA-DQ, and HLA-DR. There are two critical features of MHC molecules that determine their importance as histocompatibility antigens. First, they

are highly *polymorphic:* unlike most proteins, which are the same in all humans, such as most structural proteins and enzymes, each MHC locus can express any one of hundreds of different molecules. For example, HLA-A1, HLA-A2, HLA-A3, and so on are different enough from each other to determine self and nonself, and different molecules are expressed in each individual. Each of the MHC loci is polymorphic, and the set of different MHC molecules, or *alleles,*expressed on one chromosome is called a *haplotype*. A *genotype* is the sum of two haplotypes. The second critical feature of the MHC is that its genes are *codominantly expressed*—an individual expresses alleles from both chromosomes at each locus. Therefore, the MHC genotype of an individual consists of 12 different MHC molecules (two alleles from each of six loci). This explains why grafts from an Fl offspring are rejected by each parent: the Fl will express MHC molecules derived from both parental alleles, and the parent will recognize the other parent's alleles as foreign.

The evolutionary benefit of the extensive polymorphism of MHC molecules is that a wide variety of microbial peptides can be bound and presented to T cells, thus

successfully initiating responses to infections. However, this same polymorphism creates a practical barrier to successful organ transplantation because the chances of matching the MHC of an unrelated organ donor to that of a recipient is low. The degree of MHC matching between an allograft donor and recipient plays a role in determining the chances of a successful graft survival. In clinical transplantation, the most important MHC genes are HLA-A, HLA-B, and HLA-DR because donor-recipient mismatches at these loci have a much greater effect on risk for rejection than mismatches at the other MHC loci. The antigenic determinants of these six alleles are the focus of attempts at HLA matching to improve graft survival (see Chapter 3 and Fig. 3.3).

The molecular structure of MHC molecules has been meticulously defined. A class I molecule is composed of a polymorphic a or heavy chain (44 kDa) and a noncovalently associated invariable (nonpolymorphic) light chain, $\beta_2$microglobulin (12 kDa) (Fig. 2.1B). A class II molecule is composed of polymorphic α and β chains of similar molecular weight (32 kDa), covalently bound to each other (Fig. 2.1B). A critical feature of both classes of MHC is the presence of a peptide-binding groove (see front cover). The specific amino acids that line this groove determine which specific peptides can bind for presentation to T cells. Class I molecules bind peptides that are 9 to 11 amino acids long, whereas class II molecules bind peptides that are 13 to 30 amino acids long.

Class I and class II MHC molecules have different expression patterns. Class I molecules are expressed on essentially all nucleated cells, whereas class II molecules are expressed only on professional antigen-presenting cells (APCs), including dendritic cells, B lymphocytes, and macrophages. Cytokines play an important role in modifying the expression of MHC molecules. For example, interferons (IFNs), particularly IFN-γ, upregulate levels of MHC class I. IFN-γ also increases MHC class II levels on macrophages and can induce class II expression on cells not traditionally considered APCs, including endothelial and epithelial cells. Thus, essentially all cells in a graft can express both MHC class I and class II molecules and be potential targets of an alloresponse.

Both class I and class II molecules are stably expressed at the cell surface only if peptides are present in their binding grooves. Class I molecules bind peptides derived from proteins in the cytoplasm of cells, which are often proteins that are synthesized intracellularly, such as viral proteins (the cytosolic, or endogenous, pathway). In contrast, class II molecules bind extracellular proteins that have been brought into a cell's vesicles by endocytosis (the vesicular, or exogenous, pathway). In both cases, the complex of MHC molecule and peptide is recognized by a

T-cell receptor (TCR) to initiate T-cell activation. In the absence of a microbial infection or foreign graft, the peptides presented by MHC molecules are derived from self proteins, and some of these peptides have been shown to be derived from self-MHC molecules. The significance of the self-MHC peptides present on MHC molecules is unclear, but their possible immunologic role has led to efforts to design MHC peptide

molecules as therapies to block the rejection of allografts.

Pathways of Alloantigen Presentation

Although the immune system evolved primarily to respond to foreign microbial peptides presented by self-MHC molecules, the strong response to allografts is highly conserved in evolution. In humans, between 1% and 10% of T cells respond to a given allogeneic MHC molecule. During their maturation in the thymus, T cells that respond to self antigens are deleted (*negative selection*), whereas those that are specific for foreign peptides displayed by self-MHC molecules are allowed to develop (*positive selection*). These same positively selected T cells also recognize foreign MHC molecules in grafts and induce graft rejection. The nature of the MHC molecules recognized by alloreactive T cells varies according to the pathway of alloantigen presentation.

Direct Antigen Presentation

The response of recipient T cells to intact MHC/peptide complexes on APCs from a graft is called *direct allorecognition*. That is, the APCs in the graft directly present alloantigens (the foreign MHC molecules) for recognition by alloreactive T cells. The high alloreactivity of the T-cell repertoire is a result of cross-reactivity: T cells that normally recognize self-MHC/microbial peptide complexes (Fig. 2.2A) are also capable of recognizing foreign MHC/peptide complexes because the complexes are structurally similar. The T cells responding to direct antigen presentation recognize determinants on the allogeneic MHC molecule itself (Fig. 2.2B) as well as structures determined by both MHC and peptide (Fig. 2.2C). The peptides presented by foreign MHC molecules may be derived from polymorphic proteins (i.e., MHC antigens) or nonpolymorphic proteins (e.g., an enzyme from a metabolic pathway).

Indirect Antigen Presentation

A recipient's T cells can also respond to donor MHC peptides presented on the recipient's own APCs. This pathway is called *indirect allorecognition*, to distinguish it from the direct response to intact MHC on donor APCs (Fig. 2.3). In indirect antigen presentation, donor MHC molecules are shed from their cell surface, taken up by recipient APCs, processed, and presented as peptides on recipient MHC molecules. The indirect alloresponse is analogous to the immune response to invading microbes, which are also presented to T cells as peptides displayed by self-MHC molecules. Several types of experiments have demonstrated the importance of indirect allorecognition in graft rejection. For example, skin grafts from MHC class II-deficient mice are rejected in a CD4 T-cell-dependent manner. In this experiment, CD4 T cells (which are class II MHC restricted) cannot be stimulated by the direct pathway because no MHC class II is present on donor cells. Therefore, they must be responding to recipient APCs presenting allopeptides on recipient class II molecules.

It is generally assumed that indirect antigen presentation is more important for

activating CD4 T cells rather than CD8 T cells because class II molecules present peptides derived from exogenous sources, unlike class I molecules, which usually present peptides derived from endogenous sources. However, cross-priming of CD8 cells has been demonstrated, whereby MHC class I molecules can be loaded with peptides from exogenous sources. This suggests that CD8 cells also may be able to respond to indirect antigen presentation.

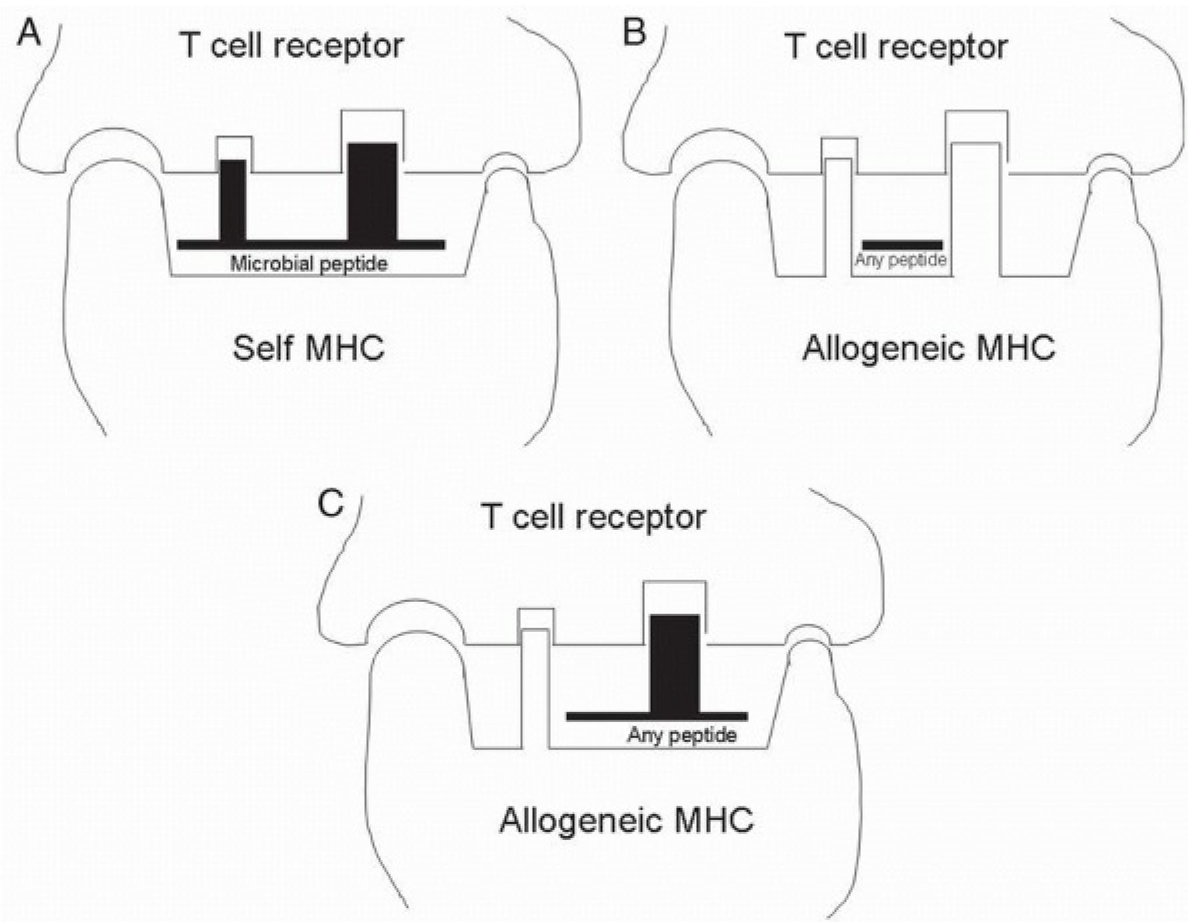


FIGURE 2.2 A: During development, T cells are selected for their ability to recognize microbial peptides (found in the central peptide groove) in the context of self MHC (identified by residues surrounding the peptide groove). These T cells cross-react with a three-dimensional structure that can be formed entirely by an allogeneic MHC molecule (**B**), or a combination of structures from the allogeneic MHC molecule and any peptide that happens to be in the peptide groove (**C**).

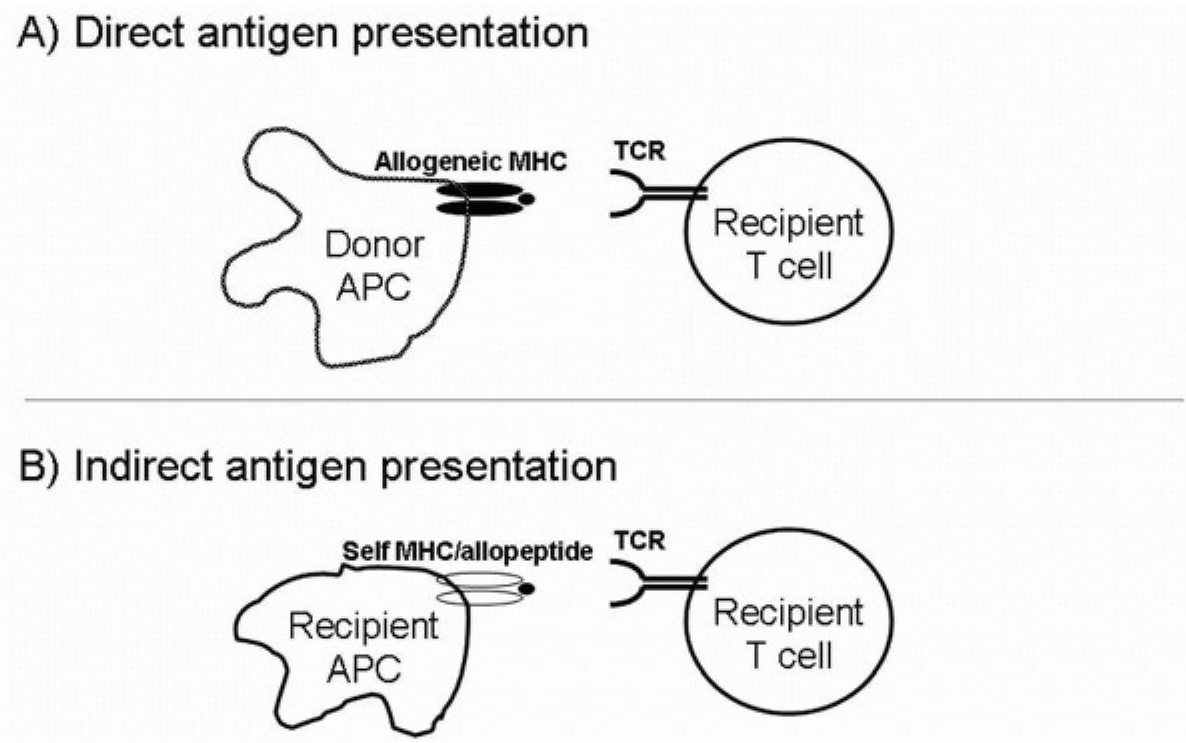


FIGURE 2.3 A: In direct antigen presentation, recipient T cells recognize intact allogeneic MHC molecules on the surface of donor APCs. **B:** In indirect antigen presentation, recipient T cells recognize allopeptides in the context of self (recipient) MHC. The allopeptides are derived from donor MHC molecules that have been processed, then brought to the cell surface by recipient MHC.

Acute rejection of an allograft is primarily dependent on direct allorecognition, with the ratio of T cells reactive by the direct pathway-to-indirect pathway ratio, estimated at 100:1. However, experimental evidence suggests that in chronic rejection, the indirect pathway may be more important. Because chronic rejection is a major cause of graft loss (see Chapter 10), there is great interest in understanding the indirect pathway with the goal of developing therapeutic approaches to block this pathway.

Minor Histocompatibility Antigens

Although the MHC is the major barrier to allotransplantation, studies in humans and mice have demonstrated that non-MHC molecules, referred to as minor histocompatibility antigens, can also mediate rejection. In fact, some mouse models of skin and cardiac transplantation have demonstrated that minor incompatibilities can lead to rejection that is as rapid as that seen in grafts with MHC mismatches. The clinical importance of minor antigens is demonstrated by the fact that MHC-matched siblings, unlike identical twins, require immunosuppression to prevent graft rejection. By definition, this alloresponse is targeting minor antigens. The mechanism of the alloresponse to minor antigens is similar to the response to microbial antigens, in that

host MHC molecules present foreign peptides to host T cells.

One example of a minor antigen is the MHC class I-related chain A (MICA) antigen. This antigen is structurally similar to MHC class I antigens and can be expressed on a variety of cells, including monocytes, epithelial cells, and endothelial cells. MICA is polymorphic and can elicit production of antibodies in transplant recipients, more so than the closely related MHC class I-related chain B (MICB) antigen. The development of anti-MICA antibodies may be associated with worse graft survival, especially in recipients of well MHC-matched kidneys.

Sites of T-cell—Antigen-Presenting Cell Interactions

After transplantation, the first foreign antigens encountered by recipient T cells are on the vascular endothelium of the graft. Resting endothelium expresses MHC class I, and activated endothelium also expresses MHC class II molecules. Not surprisingly, inflammation of the endothelium, referred to as *endotheliitis*or *vasculitis,* is one of the hallmarks of acute graft rejection (see Chapter 14).

In addition, when an organ is transplanted, donor leukocytes are carried to the recipient as passenger leukocytes with the graft. These leukocytes are found in lymphoid tissue and in most other organs of the body, scattered within the parenchyma. The most important of these cells are dendritic cells, which are potent APCs because of their ability to express high levels of MHC molecules as well as critical accessory molecules that facilitate T-cell activation. Passenger leukocytes play an important role in allograft rejection, and in several models, the removal of these cells before transplantation prolongs graft survival. For example, both the culture of thyroid cells before transplantation and the use of antibodies to deplete dendritic cells from islet allografts prolong graft survival.

Passenger leukocytes may stimulate direct alloresponses of graft-infiltrating T cells and may also shed MHC molecules that can be taken up and presented by infiltrating monocytes, thereby stimulating an indirect alloresponse of infiltrating T cells. In addition, passenger dendritic cells are able to migrate out of a graft and traffic to recipient lymphoid tissue, where they can again elicit either a direct or indirect alloresponse. Thus, the recipient's lymphoid organs are also an important site of T cell-APC interactions.

Role of Graft Injury and Ischemia in the Alloresponse

The surgical procedure required to transplant a graft produces an inflammatory response to the injury as well as to the ischemia that develops in the organ before its vessels are reconnected. This process, also referred to as *ischemia-reperfusion*, is chronologically the first event after transplantation, and its importance has been clearly demonstrated using syngeneic grafts. In particular, the process of cutting and

reattaching vessels, restoring blood flow to an ischemic organ, leads to the production of inflammatory cytokines and the recruitment of cells such as macrophages into the graft. Thus, the immune response is primed, so that antigen-reactive cells are also recruited to the site of injury. If no alloantigens are encountered, as in a syngeneic graft, the inflammatory response subsides with a time course similar to that of any repair from injury. But if alloantigens are present, the antigen-specific immune response leads to graft rejection. The clinical importance of graft ischemia is highlighted by studies showing that acute rejection episodes are more frequent with grafts having prolonged ischemia time before transplantation. In addition, living unrelated kidney transplants (which are completely MHC mismatched but have short ischemia time) are often more successful than well-matched deceased donor transplants, which have more prolonged ischemia time (see Chapter 3).

Innate Versus Adaptive Immunity

Ischemia-reperfusion injury is one example of antigen-independent immune responses that have been termed *innate (or natural) immunity*, as opposed to the MHC-specific responses of *adaptive immunity*. Although adaptive immunity is found in vertebrates, innate immunity is found in almost all multicellular organisms. Innate immunity is a more primitive form of response but is important both for immunity to infections and in transplantation. Innate immune responses occur first and can affect the nature of subsequent adaptive immune responses. Innate immunity involves neutrophils, macrophages, natural killer cells, cytokines, and complement components. A number of toll-like receptors (TLRs) have been identified as playing an important role in innate immune responses. Adaptive immunity is mediated by antigen-specific T and B lymphocytes but interacts closely with innate immunity because activated lymphocytes produce cytokines and activate cells and mediators of the innate immune system.

Leukocyte Recruitment

For a leukocyte to exit from a blood vessel and home in on a site of tissue injury, such as an allograft, a complex series of interactions between *adhesion*molecules must take place. Leukocyte homing can be divided into three steps (Fig. 2.4). In the first, endothelial cells are activated, leading to the expression of *selectins*. The binding of selectins to their ligands on leukocytes slows their flow, and the leukocytes start rolling along the endothelium. This step allows circulating cells to sample various environments. The second step involves the secretion of *chemokines (chemotactic cytokines)*, which attract more leukocytes to the site of inflammation and leads to the firm attachment of leukocyte to endothelium. This firm adhesion is mediated by *integrins* on leukocytes binding to their ligands, either on the endothelial cell surface or in the extracellular matrix. The third step is the extravasation of leukocytes into surrounding tissue. One of the most extensively studied adhesive interactions is that between the integrin leukocyte factor antigen-1 (LFA-1) (CDlla/CD18) and intercellular adhesion molecule-1 (ICAM-1 (CD54). In addition to their role in antigen-independent

processes such as leukocyte extravasation, LFA-1 and ICAM-1 are also important in antigen-specific immune responses because they mediate adhesion between T cells and APCs.

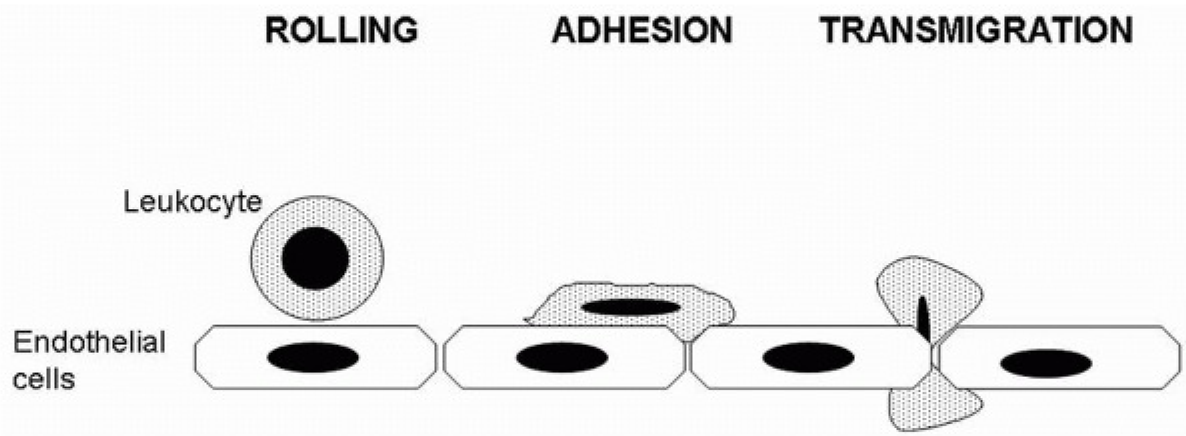


FIGURE 2.4 Leukocyte recruitment. Expression of selectins slows the flow of leukocytes in blood vessels and causes them to roll along the endothelium. Release of chemokines activates the leukocytes, and expression of high-affinity integrins causes firm adhesion to endothelial cells. Firmly adherent cells then transmigrate through the endothelial cell layer into the interstitial site of injury.

Many of the steps involved in leukocyte recruitment have been studied specifically in the context of transplantation. Ischemic injury causes increased production of several cytokines, including interleukin-1 (IL-1), which upregulates expression of selectins. Cytokines produced following the trauma of transplantation also induce expression of several other adhesion molecules, including E-selectin, ICAM-1, and vascular cell adhesion molecule-1 (VCAM-1. Chemokines are also upregulated in the context of graft infiltration. Several adhesion molecules have been studied as potential targets to block graft rejection. For example, antibodies to LFA-1 or ICAM-1 prolong graft survival in animals, and preliminary studies in humans show promise in mitigating rejection.

LYMPHOCYTE ACTIVATION

T Lymphocytes

The critical importance of T cells in the rejection of allogeneic grafts has long been recognized from diverse models in which T cells are genetically absent or impaired. T-cell recognition of alloantigen is the primary event leading to activation, proliferation, and differentiation of alloreactive T cells and to T-celldependent rejection.

The T-Cell Receptor for Antigen

The TCR is a heterodimer composed of an α and a β polypeptide chain, both of which have variable (V) and constant (C) domains. Additional diversity in the peptide-binding region, which includes the V domain, is provided by joining (J) segments and, on the β chain only, a diversity (D) segment. A second TCR heterodimer, comprising γ and δ chains, has been described, but has not been shown to play a role in the alloresponse. TCRs are associated on the T-cell surface with the CD3 complex, made up of several polypeptide chains that are important for the cell surface expression of the TCR, and for transmitting signals into the T cell. The critical importance of $CD3^+$ cells is demonstrated by the fact that one of the most potent immunosuppressive agents used in clinical transplantation is muromonab OKT3, which binds to and inactivates T cells (see Chapter 5).

Intracellular Signaling

To transduce molecular events at the surface of T cells into the nucleus and modify the expression of genes that regulate cell function, a complex machinery

---

is required. A number of signaling pathways have been identified in T cells, and many steps in these pathways have been targets for blocking the alloresponse. Engagement of the TCR induces phosphorylation of TCR-associated proteins such as the σ (zeta) chain, as well as a variety of adapter proteins. These phosphorylation events lead to the activation of several biochemical pathways, including the calcineurin pathway, the protein kinase C pathway, and the Rasand Rac-mitogen-activated protein (MAP) kinase pathways.

Of these pathways, the calcineurin pathway (Fig. 2.5) is the best characterized because it is the site of action of the potent immunosuppressive agents cyclosporine and tacrolimus. Within minutes of TCR engagement, phosphorylation of ZAP-70 (σ-associated protein of 70 kDa) leads to the phosphorylation of PLCγ1 (phospholipase C γ1), which hydrolyzes a membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 leads to an increase in cytosolic calcium, which binds calmodulin, forming a complex that activates several enzymes, including the phosphatase calcineurin. Calcineurin dephosphorylates NFAT (nuclear factor of activated T cells), allowing NFAT to translocate from the cytoplasm to the nucleus. Once in the nucleus, NFAT binds to regulatory sequences and increases the transcription of genes for several cytokines, including the T-cell growth factor, IL-2. Cyclosporine exerts its immunosuppressant effect by binding to an intracellular protein, cyclophilin, and the cyclosporine/cyclophilin complex inhibits the activity of calcineurin. Tacrolimus (originally known as “FK”) binds to FK-binding protein (FKBP) and the tacrolimus/FKBP complex similarly inhibits the activity of calcineurin (See Plate 5.1). Hence the drugs are both referred to as *calcineurin*

inhibitors (see Chapter 5).

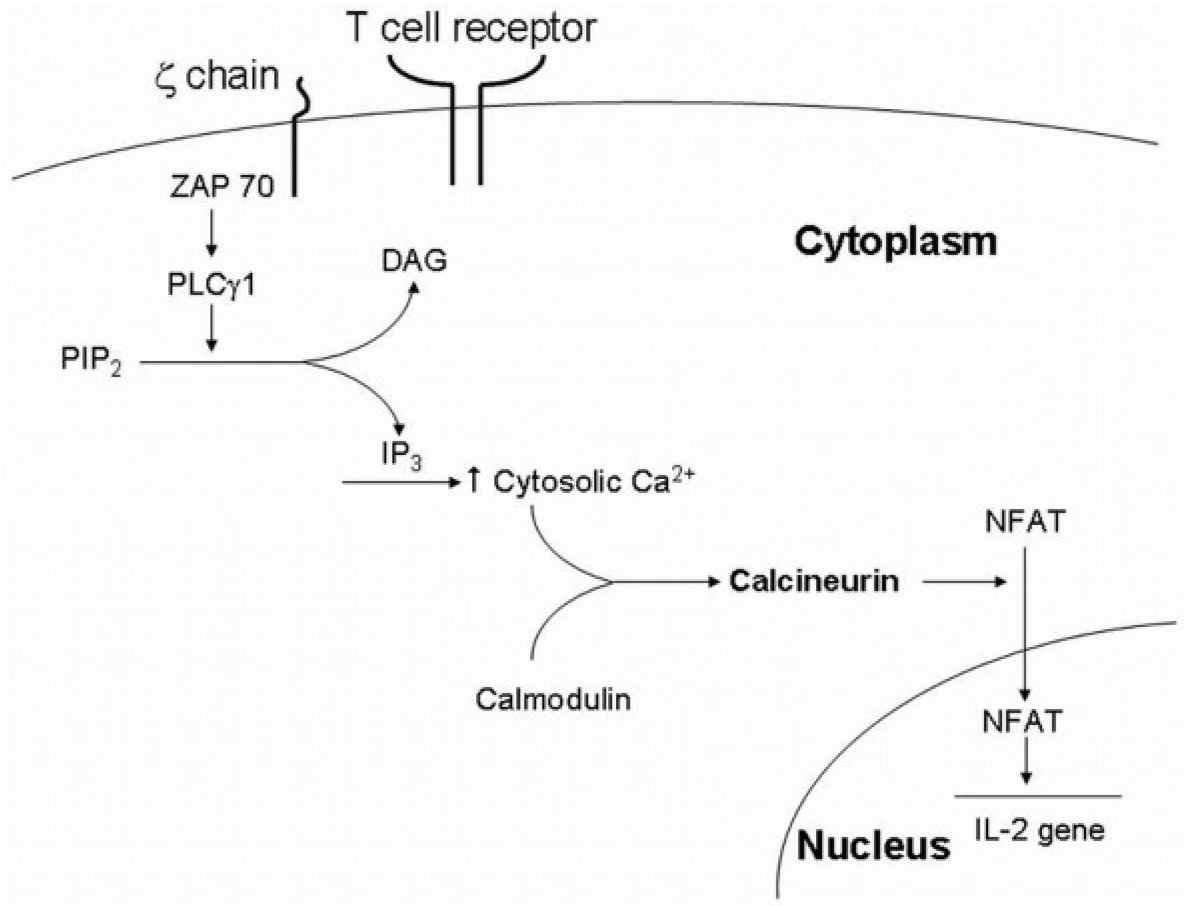


FIGURE 2.5 Intracellular signaling in T cells, one of the many signal cascades by which cell surface events are transduced into cellular changes. The activation of calcineurin is inhibited by cyclosporine and tacrolimus, decreasing T-cell production of IL-2 and other cytokines, and thus impairing T-cell proliferation. DAG, diacylglycerol; IL-2, interleukin-2; IP_3, inositol 1,4,5-trisphosphate; NFAT, nuclear factor of activated T cells; PIP_2, phosphatidylinositol 4,5-bisphosphate; PLCγ1, phospholipase C γ1; ZAP-70, σ-associated protein of 70 kDa.

CD4 and CD8 Subsets of T Cells

Most mature T cells carry either the CD4 or CD8 protein on their cell surface. CD4 molecules define the "helper" subset of T cells and directly bind MHC class II molecules, thus restricting CD4 T cells to MHC class II. CD8 molecules define the "cytolytic" subset of T cells, and directly bind MHC class I molecules, thus restricting CD8 T cells to MHC class I. However, exceptions to this functional division of T cells exist. For example, CD4 cells restricted to MHC class II, in certain systems, have cytolytic function, and CD8 cells produce many, although not all, of the regulatory cytokines made by CD4 cells.

Generally, CD4 T cells are thought to mediate the initial recognition of an allograft and to help amplify and coordinate the subsequent immune response, including providing help to CD4 and CD8 effector T cells. For example, in a model of mouse heart transplantation, CD4-deficient mice are unable to reject grafts, whereas CD8-deficient mice do reject grafts. This is one of several models in which a CD4 T-cell-mediated delayed-type hypersensitivity (DTH) response is sufficient to cause rejection, without requiring the cytolytic function of CD8 cells. However, in other experimental models, antibody blockade of CD8 cells prevents rejection, suggesting the need for CD8 cells to destroy a graft. Taken together, these data are a testament to the overlapping functions, or redundancy, of various components of the alloresponse and the ability of the immune system to compensate for specific impairments and still cause the destruction of a transplanted organ.

Type 1 and Type 2 T-Cell Responses

On activation, T cells produce a variety of cytokines to regulate the immune response. With persistent antigenic stimulation, T cells can often be shown to differentiate into one of two different types with distinct cytokine profiles. Type 1 helper T cells (called Th1 cells) secrete cytokines that include IL-2, IFN-γ, IL-12, and tumor necrosis factor (TNF). These cytokines stimulate DTH reactions, cytolytic activity, and production of opsonizing and complement-fixing IgG antibodies. Type 2 helper cells (Th2 cells) secrete cytokines that include IL-4, IL-5, IL-10, and IL-13, which activate eosinophils and stimulate production of immunoglobulin E (IgE) antibody. The regulation of these two types of responses has been most extensively studied in CD4 helper cells, but the polarization of responses also appears to apply to CD8 cytolytic cells. IFN-γ and IL-12 promote deviation to type 1 responses, whereas IL-4 promotes type 2 responses. In addition, IFN-γ inhibits type 2 responses, whereas IL-4 inhibits type 1 responses, so that responses become increasingly polarized once they are initiated.

It has been hypothesized that Th1 responses lead to rejection, whereas Th2 responses might mediate tolerance of grafts. This hypothesis developed in part from the findings that type 1 cytokines promote effector functions such as DTH and cytolytic activity, whereas type 2 cytokines antagonize these activities. Several experimental studies have shown that acute rejection is associated with an expansion of type 1 cytokines, whereas prolonged survival is associated with reduced levels of these cytokines. However, other studies have shown that rejection is associated with the production of both type 1 and type 2 cytokines, whereas tolerance is associated with a decrease in both types of cytokines. For now, attempts to effect graft rejection by manipulating cytokines have been largely unsuccessful. However, ongoing studies continue to define new cytokines and their roles in immune responses. For example, a third type of cytokine profile has been reported in cells that produce IL-17. This Th17 response appears to have a strong inflammatory effect and may potentially become a target of antirejection therapies.

T-Cell Costimulation

The specificity of the immune response is determined by the interaction between the TCR of a T cell and the MHC/peptide complex on an APC. However, several other molecular interactions between T cells and APCs are essential for T-cell activation (Table 2.1). T-cell activation requires one signal through the TCR and a second, or costimulatory, signal through accessory molecules. These accessory molecules play two important roles. The first role is to provide adhesive strength to keep the T cells and APCs in contact with each other, thus providing time for the TCR to sample antigens on the APC. Integrins, particularly LFA-1 on T cells binding to ICAMs on APCs, are among the most important adhesion molecules for T-cell activation. The second role of accessory molecules is to cooperate with TCR-initiated signals in the process of T-cell activation. The most potent second signals regulating T-cell clonal expansion and differentiation are provided by the B7/CD28 family of molecules.

CD28 is expressed on most T lymphocytes, and engagement of CD28 increases T-cell proliferation by a variety of mechanisms, including the production of IL-2 and other cytokines. APCs express two ligands for CD28: B7-1 (CD80) and B7-2 (CD86). Expression of both B7 molecules is upregulated on APCs that have been activated by a variety of inflammatory stimuli, including microbial infection and cytokines. B7-1 and B7-2 can both provide T-cell costimulation through CD28, but they have distinct patterns of expression and binding kinetics for CD28, suggesting significant differences in their roles. B7-1 and B7-2 also regulate T cells by binding cytotoxic T-lymphocyte antigen-4 (CTLA-4, which inhibits T-cell proliferation.

The immunosuppressive drugs in current use are extremely potent in blocking transplant rejection, but none of these drugs is antigen specific, so they also strongly suppress immune responses to infections. Therefore, the goal of transplantation immunology is to specifically block responses to transplantation antigens, without producing global immunosuppression. One approach to this goal is to induce T-cell anergy, or antigen-specific unresponsiveness. *In vitro* models demonstrate that one way to induce anergy is to provide a T-cell with an antigen-specific signal through its TCR in the absence of CD28 engagement (Fig. 2.6). In these models, subsequent exposure of the cell to both TCR and CD28 signals no longer can activate the T cell. Targeting the B7/CD28 pathway holds great promise for achieving antigen-specific unresponsiveness because the timing of transplantation can be controlled so as to coincide with the administration of agents that block CD28 engagement. If blockade of CD28 were only required at the time of initial antigen exposure, a graft recipient would not be exposed to the infectious risks of long-term immunosuppression. In addition, T-cell responses to transplant antigens could be prevented, without the need to identify the specific antigen.

TABLE 2.1 Some Critical T-Cell Accessory Molecules and Their Ligands

T Cell	APC
TCR	MHC/peptide
CD28	B7-1/B7-2
LFA-1	ICAM-1
CD2	LFA-3
CD4	MHC class II
CD8	MHC class I

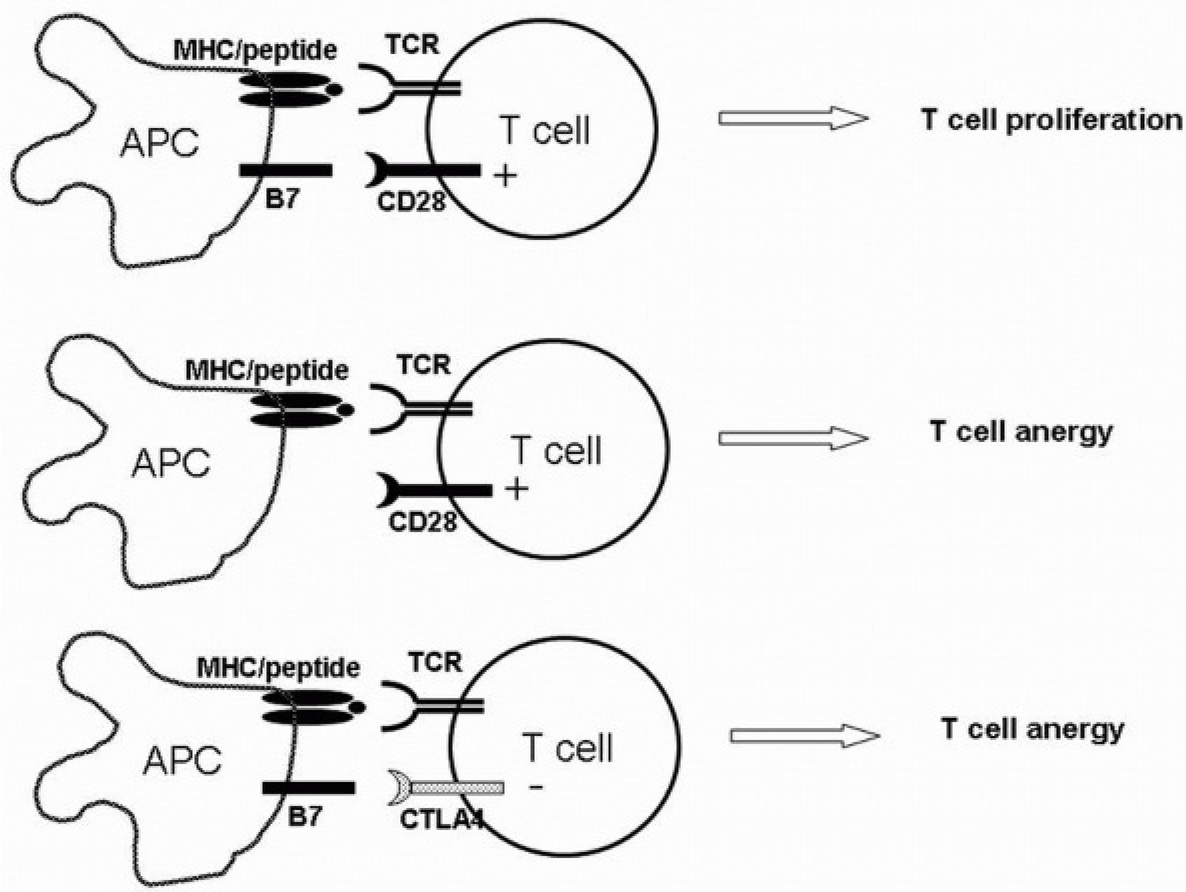


FIGURE 2.6 T cells require costimulation for activation. If both TCR and CD28 are engaged, T cells proliferate and differentiate. If the TCR is engaged in the absence of B7 costimulation, T cells fail to proliferate and become anergic. Binding of B7 to CTLA-4 is also important in inducing anergy.

In a wide variety of experimental models in animals, and in preliminary human trials, blockade of B7 molecules has been shown to significantly prolong graft survival. However, in most *in vivo* models of B7 blockade, anergy limited to specific antigens has been difficult to demonstrate. One reason for this difficulty may be the complexity of costimulation. For example, there is increasing evidence that engagement of CTLA-4 is important in inducing tolerance (Fig. 2.6). Because B7 blockade affects signaling through both CD28 and CTLA-4, and these molecules have opposing effects, the net result is highly dependent on the experimental system. Manipulation of this pathway may also be complicated by the existence of additional molecules, homologous to B7 or to CD28, that have been recently discovered. These molecules of the CD28 superfamily transduce both stimulatory and inhibitory signals to T cells (Fig. 2.7, left side). For example, B7h on APCs stimulates T cells by binding ICOS (inducible costimulator), and PD-L1 and PD-L2 inhibit T cells by binding PD-1. The interaction between these pathways is still being defined, but understanding their regulation is likely to improve therapies targeting costimulation.

Another molecular interaction that is critical in immune responses is that between the

CD40 molecule on APCs and CD40 ligand (CD 154, CD40L) on T cells. CD40 engagement plays a critical role in activating B cells, dendritic cells, and monocytes and also upregulates expression of the B7 molecules. B7 interactions with CD28 and CTLA-4, in turn, are critical in T-cell regulation. There is also some evidence that engagement of CD154 directly stimulates T cells. The CD40/CD154 pathway has been the subject of great interest because of its importance in the activation of both APCs and T cells, and blockade of this pathway in experimental models of transplantation has proved to be extremely

effective. In addition, a number of other pathways in the same family as CD40/CD154, the TNF/TNFR (tumor necrosis factor receptor) family, are also important in T-cell-APC interactions (Fig. 2.7, right side). In experimental models, blockade of TNF and CD28 superfamily pathways appears to be synergistic, and this approach has already shown potential clinical applicability in studies of nonhuman primates.

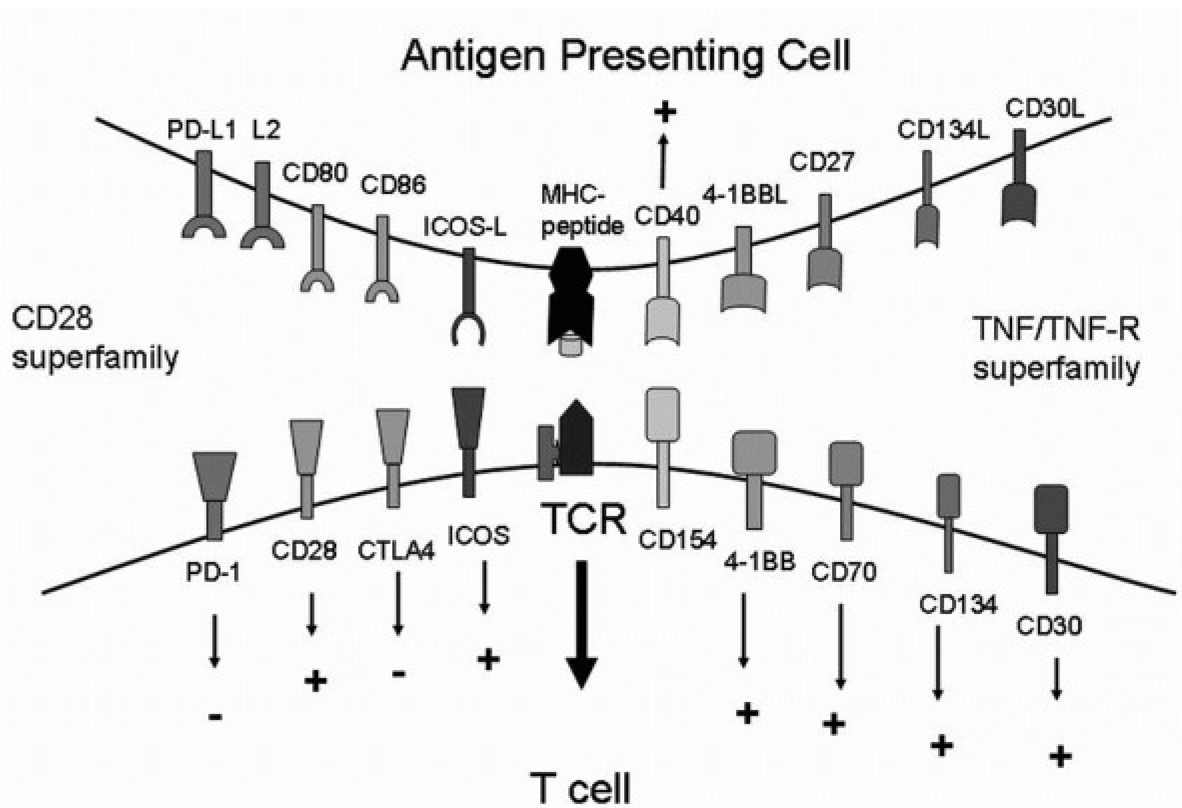


FIGURE 2.7 Schematic of major costimulatory molecules belonging to the CD28 and TNF/TNFR superfamilies. Signals transduced into cells can either be stimulatory (+) or inhibitory (-). ICOS, inducible costimulator; TNFR, tumor necrosis factor receptor.

B Lymphocytes

The importance of B cells and antibodies in the rejection of an allograft is most

dramatically illustrated by hyperacute rejection. This process occurs within 24 hours of transplantation in patients who were previously sensitized and developed antibodies to ABO blood group antigens or to allogeneic MHC molecules through previous transplants, blood transfusions, or pregnancy (see Chapter 3). Currently, hyperacute rejection is rare because ABO blood typing and a crossmatch test to detect these antibodies are performed before proceeding with renal transplantation. However, some episodes of antibody-mediated rejection occur later than 24 hours after transplantation, presumably because low antibody levels may be missed by crossmatching, or because of reactivation of memory B cells. More common than pure antibody-mediated rejection however, is mixed cellular and antibody-mediated rejection. The cellular component is mostly mediated by T cells, which activate B cell to produce antibodies that contribute to allograft destruction. The antibody component of rejection is best identified in biopsy specimens by the presence of the complement protein C4d. Although the histologic findings in these cases are variable, the presence of C4d appears to correlate with the presence of donor-specific antibodies (see Chapter 14). Antibodies may also play an important role in chronic rejection. Both acute and chronic antibody-mediated rejection can potentially be treated with biologic agents that target the B-cell-specific marker, CD20 (see Chapter 5).

EFFECTOR MECHANISMS OF GRAFT DESTRUCTION

Once CD4 T cells recognize foreign class II MHC molecules, they play a critical role in regulating various arms of the effector response. The initial *innate immunity* inflammatory response to the injury associated with transplantation is antigen independent. The antigen-specific activation of CD4 T cells leads to expression of cell surface molecules and production of cytokines, which, in turn, further stimulates monocytes. This cooperation between CD4 T cells and monocytes, or DTH response, plays an important role in the destruction of a graft.

The activation of CD4 T cells and production of cytokines also stimulates the activation and proliferation of cytolytic CD8 T cells and natural killer (NK) cells. On recognition of class I MHC molecules on graft cells, the CD8 T cells cause cell death by two main mechanisms. The first mechanism is the release of soluble cytotoxic factors such as granzymes and perforin. The second mechanism is the upregulation of Fas ligand on T cells, which binds Fas (CD95) on target cells. When Fas is engaged on cells of a graft, these cells undergo apoptosis, or programmed cell death.

The production of cytokines by CD4 T cells also stimulates B cells. On binding of specific antigen by the B-cell receptor, or cell surface immunoglobulin, B cells proliferate and differentiate into plasma cells. Plasma cells release soluble immunoglobulins, or antibodies, which can bind allogeneic cells. Antibodies can cause cell damage by fixing complement or by mediating antibodydependent cellular cytotoxicity (ADCC).

TOLERANCE

Tolerance broadly refers to the absence of immune responses to specific antigens. During development, one of the critical functions of immune system is to prevent responses directed toward self antigens, thus preventing autoimmune disease. This is achieved both by *central tolerance* in the thymus and by *peripheral tolerance* in extrathymic lymphoid tissue. During T-cell development, most T cells found in the thymus have undesirable reactivities, so are deleted or made unresponsive by negative selection. T cells that recognize foreign antigen in the context of self MHC are positively selected and allowed to circulate in the blood. The process of negative selection is imperfect, so autoreactive T cells can be found in the periphery. Autoimmunity is usually prevented by the process of peripheral tolerance.

Peripheral tolerance is maintained by a number of mechanisms, including clonal deletion, anergy, and suppression. In contrast to clonal deletion of T cells, anergic T cells are still present but unable to respond, for example, because of the absence of costimulatory signals. The phenomenon of suppressor cells has long been demonstrated by adoptive transfer experiments, in which transfer of cells from tolerant animals can induce tolerance in naive animals. The molecular phenotype of suppressor cells, including their cell surface molecules and soluble factors produced, is an area of active research. For example, regulatory T cells (Tregs) express CD4, the IL-2 receptor α chain CD25, and the transcription factor FOXP3 and appear to be important in suppressing a variety of immune responses.

In the context of transplantation, *tolerance* can be defined as the absence of a destructive immune response to a graft, in a host with otherwise intact immunity. This is a critical goal because transplant recipients are otherwise subjected to global immunosuppression that leaves them at increased risk for infections and malignancies. A variety of experimental approaches have tried to take advantage of basic mechanisms of tolerance in an attempt to induce transplantation tolerance. Early animal studies demonstrated that intrathymic

---

injection of soluble antigen can induce central tolerance. Tolerance has also been induced by ablation or immunosuppression of a recipient's immune system and reconstitution with both donor and recipient bone marrow, thus generating a chimeric immune system that does not reject donor organs. Some success has been reported using nonmyeloablative treatments of recipients who received combined kidney and bone marrow transplants. These recipients were able to entirely stop immunosuppressant medications, but many details of the type, dose, and timing of the preparative regimens need to be improved, to navigate between the potential high morbidity of aggressive therapies and the potential high rejection rates of less aggressive treatments.

A variety of approaches have been taken to inducing peripheral tolerance. For

example, T-cell deletion has been induced by programmed cell death, or apoptosis. The blockade of T-cell costimulatory signals has induced anergy, and the manipulation of the cytokine environment has suppressed T-cell activation. Novel strategies have used the immunomodulatory effects of peptides derived from amino acid sequences found in MHC molecules.

Despite the success of many potent immunosuppressive regimens in prolonging graft survival, the acquisition of antigen-specific tolerance remains a goal, rather than the clinical reality of transplantation. However, approaches to tolerance induction in animal models are increasingly successful in achieving this goal, and many of these approaches are approaching human trials. The term *near tolerance* has been used to describe the situation that is achieved when a graft continues to function well in the face of minimal immunosuppression or after discontinuation of immunosuppression. Early clinical trials suggest that in the short-term this may be a more realistic goal than the much sought after full tolerance.

IMMUNOLOGIC MONITORING

The clinical diagnosis of renal allograft rejection currently relies on the histologic evaluation of a biopsy specimen. Because biopsies are usually performed only after a rise in creatinine is observed, several days and often weeks elapse between the start of graft rejection and the initiation of treatment. This delay allows tissue to be damaged and shortens the survival of the graft. Biopsies are also not ideal as a technique to diagnose rejection because they are invasive, so they cannot be repeated as frequently as desired to closely monitor a graft. As a result, several approaches have been attempted to monitor the immune response to a graft noninvasively. Ideally, an immune assay would detect rejection in its earliest stages. In addition, it would allow the accurate monitoring of the alloresponse so that immunosuppression could be adjusted to minimize exposure of the patient to side effects while maximally preserving the graft.

The most commonly used immune monitoring in clinical renal transplantation is the measurement of donor-specific antibodies (DSA). These antibodies to donor MHC can be detected and quantified before or after transplantation by either cytotoxicity or flow cytometry. The presence of DSA after transplantation is critical to the diagnosis of antibody-mediated rejection and may prove useful in assessing chronic rejection. However, these assays do not reliably correlate with overall alloreactivity, because of the importance of cellular responses.

One of the oldest assays of cellular alloreactivity is the mixed lymphocyte response (MLR). In this assay, cells from the donor are inactivated and then mixed with lymphocytes from the recipient or responder. The degree of proliferation of responder cells, which are mostly CD4 T cells, reflects alloreactivity. A related assay is the cell-mediated lympholysis (CML), which measures the killing of donor cells by CD8 T cells. The MLR and CTL assays are essentially *in vitro* versions of *in vivo* transplantation and

models. However, their clinical utility in renal transplantation is limited because of the many examples in which the MLR and CML do not correlate with clinical rejection.

Immune reactivity has also been assayed by mixing a transplant recipient's T cells with peptides that correspond to donor MHC molecules. These peptides can be designed to reflect indirect antigen recognition, and reactivity to these peptides may prove to be particularly useful in predicting chronic rejection.

Another approach has been to measure the frequency of alloreactive T cells per volume of blood. In particular, an enzyme-linked immunospot (ELISPOT) assay for IFN-γ-producing cells is able to accurately quantitate small numbers of alloreactive T cells responding either to cells or peptides. However, the correlation between IFN-γ-producing cells and clinical transplant rejection remains to be proved.

One of the most promising recent developments in immune monitoring is the measurement of expressed genes (genomics) or proteins (proteomics) associated with immune responses. For example, renal biopsy levels of messenger RNA for perforin, granzyme B, and Fas-L correlate well with the histologic diagnosis of rejection. The correlation with rejection is particularly strong if more than one of these three cytotoxic mediators is elevated. The utility of these measurements for the noninvasive diagnosis of rejection has been studied in samples obtained from blood and from urine.

Although noninvasive assays of rejection have yet to be clinically used, it is likely that in the future such an assay, or possibly a panel of available assays, will greatly improve the management of immunosuppression in renal transplant recipients. In addition, such assays should be critical in evaluating novel immunosuppressive drugs and regimens.

XENOTRANSPLANTATION

Xenotransplantation involves the transplantation of tissues between different species. Initial interest was based partly on ethical concerns about using organs from humans. Currently, organs transplanted from animals to humans are viewed as a potential solution to the severe shortage of organs. Several major hurdles remain to the clinical application of xenotransplantation. From a public health point of view, the greatest concern is that novel infectious agents might be introduced from animals into human populations. In addition, immune responses to xenografts have several unique features not present in responses to allografts. For example, primates reject pig kidneys in a hyperacute fashion as a consequence of preformed antibodies to cell surface sugars such as Galalpha(1-3)-Gal. These xenoreactive natural antibodies are similar to the isohemagglutinins that recognize blood groups A and B, and the hyperacute rejection they produce is dependent on activation of complement. Porcine xenografts are particularly susceptible to complement-mediated injury because they lack the complement regulatory proteins (such as decay accelerating factor) that are present on human tissues.

A number of approaches have been used to prevent hyperacute rejection of xenografts. These include depleting xenoreactive antibodies from the recipient's circulation and administering reagents that inhibit complement. Genetic modification of porcine grafts also shows promise because kidneys from transgenic pigs expressing human complement regulatory proteins minimize hyperacute rejection, and knockout pigs that lack Gal-alpha(1-3)-Gal have now been generated.

If hyperacute rejection of xenografts could be entirely prevented, they would still be susceptible to acute vascular and cellular rejection. Antigens targeted by vascular rejection include MHC molecules and other xenoantigens found on endothelium. The effectiveness of currently available immunosuppressant strategies in blocking acute rejection of xenografts is being explored.

CONCLUSIONS

The past 20 years has seen an explosion of knowledge about the molecular interactions responsible for immune responses to allografts. MHC molecules are known to play a role in immune responses to all microbes but were originally described as transplantation antigens and continue to play a critical role as such. The recognition by the TCR of MHC/peptide complexes is the central antigen-specific event in the response to grafts, but the fact that each graft expresses a unique set of antigens has made the development of broadly applicable therapies targeting the MHC extremely difficult. Lymphocyte activation is a complex process, and many molecular interactions have been described. New interactions continue to be reported, and further work is required in understanding the interactions between various pathways as well as areas of redundancy. Many of these molecules have been considered as targets for therapy of transplant rejection, and the years to come are likely to yield continued progress in developing increasingly specific treatments, with concomitant decreases in toxicities.

Selected Readings

Andrade FC, Waddell TK, Keshavjee S, Liu M. Innate immunity and organ transplantation: the potential role of toll-like receptors. Am J Transplant 2005;5:969-975.

Anglicheau D, Sharma V, Ding R et al. MicroRNA expression profiles predictive of human renal allograft status. Proc Natl Acad Sci 2009;106:5330-5335.

Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006;441:166-168.

Briscoe DM, Sayegh MH. A rendezvous before rejection: where do T cells meet transplant antigens? Nat Med 2002;8:220-221.

Delves PJ, Roitt IM. The immune system. Part I. N Engl J Med 2000;343:37-49.

Delves PJ, Roitt IM. The immune system. Part II. N Engl J Med 2000:343:108-117.

Hancock WW, Wang L, Ye Q, et al. Chemokines and their receptors as markers of allograft rejection and targets for immunosuppression. Curr Opin Immunol 2003;15:479-486.

Kawai T, Cosimi B, Spitzer T. HLA-mismatched renal transplantation without maintenance immunosuppression. N Engl J Med 2008;358:353-361

Mandelbrot DA, Sayegh MH. Novel costimulation pathways. Curr Opin Organ Transplant 2003;8:25-33.

Marrack P, Kappler J. The antigen-specific, major histocompatibility complex-restricted receptor on T cells. Adv Immunol 1986;38:1-30.

Salama AD, Womer KL, Sayegh MH. Clinical transplantation tolerance: many rivers to cross. J Immunol 2007;178:5419-5423.

Sayegh MH, Turka LA. The role of T-cell costimulatory activation pathways in transplant rejection. N Engl J Med 1998;338:1813-1821.

Sayegh MH. Why do we reject a graft? Role of indirect allorecognition in graft rejection. Kidney Int 1999;56:1967-1979.

Schwartz RS. Diversity of the immune repertoire and immunoregulation. N Engl J Med 2003;348:1017-1026.

Snadling J, Busque S, Dejbakhsh-Jones S, et al. Tolerance and chimerism after renal and hematopoietic-cell transplantation. N Engl J Med 2008;358:362-368.

Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. Cell 1994;76:301-314.

Starzl TE. Immunosuppressive therapy and tolerance of organ allografts. N Engl J

Med 2008;358:407-411.

Strom TB, Suthanthiran M. Prospects and applicability of molecular diagnosis of allograft rejection. Semin Nephrol 2000;20:103-107.

Takemoto SK, Zeevi A, Feng S, et al. National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant 2004;4:1033-1041.

Wu Z, Bensinger SJ, Zhang J, et al. Homeostatic proliferation is a barrier to transplantation tolerance. Nat Med 2004;10:87-91.

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

3

Histocompatibility Testing, Crossmatching, and Immune Monitoring

J. Michael Cecka

Raja Rajalingam

Jennifer Zhang

Elaine F. Reed

Tissues and organs transplanted from one individual to another genetically disparate individual are rejected unless immunosuppressive medications are given. The recipient's lymphocytes recognize cell surface proteins of the grafted tissue that are different from the recipient and trigger immune responses leading to rejection. Human leukocyte antigen (HLA) expressed on the surface of the graft provokes the most severe immune rejection, and the gene family encoding HLA molecules has been named the major histocompatibility complex (MHC). The similarity between the constellation of HLA antigens of the donor and recipient (the degree of histocompatibility) affects long-term graft survival, and for that reason, HLA matching has been incorporated into kidney allocation in the United States and in many other countries (see Chapter 4). Antibodies directed against mismatched donor HLA antigens that might arise as a result of pregnancies, blood transfusions, or transplantation cause hyperacute or accelerated acute graft rejection when they are present before transplantation. Additionally, recent evidence implicates their appearance after transplantation with accelerated acute rejection and with chronic graft dysfunction and loss (see Chapter 14). This chapter describes the HLA antigens and their genetics, methods to identify them, anti-HLA antibodies and the means to detect and characterize them, and the important role each plays in kidney transplantation.

THE MAJOR HISTOCOMPATIBILITY COMPLEX

Human MHC Gene Cluster

The human MHC comprises about 3.6 Mb DNA (0.1% of the genome) located on chromosome 6p21.31. The MHC is the most gene-dense region of the human genome

comprising more than 220 genes. The average gene density over the entire MHC region is one gene per 16 kilobases (kb). Only 50% of the genes in MHC region appear to be expressed, and the remainder are unexpressed pseudogenes. One possible explanation for maintaining such high levels of pseudogenes could be that they are involved in generating new alleles by gene conversion, a phenomenon that has been observed at other human immune loci. About 40% of the expressed genes have immune system function.

The human MHC has been divided physically into three regions: class I (telomeric), class II (centromeric), and class III (central region, see Chapter 2, Fig. 2.1). The HLA class I cluster comprises three classic class I genes (HLA-A, -B, and -C), three nonclassic class I genes (HLA-E, -F, and -G), two class I-like genes (MHC class I-related chain A [MICA] and MHC class I-related chain A [MICB]), and several pseudogenes. The classic class I genes are constitutively expressed by all nucleated cells and control the activation and function of cytotoxic T lymphocytes. The expression of nonclassic class I antigens is restricted to specific tissues, whereas the class I-like genes are expressed under some physiologic stress conditions. The products of both nonclassic and class I-like genes serve as ligands to receptors that control the function of natural killer cells.

The HLA class II cluster comprises classic class II genes (HLA-DR, -DP, and -DQ), nonclassic class II genes (HLA-DM and -DO), and several pseudogenes. The HLA-DR region contains one functional gene for the α chain (DRA) but has one or two functional genes for the β chain, depending on the HLA-DR type. All HLA-DR types have the DRB1 gene, and some contain an additional functional DRB gene, DRB3, DRB4, or DRB5, which forms a second cell surface heterodimer with the DRA-encoded α chain. HLA class II molecules are constitutively expressed by antigen-presenting cells (dendritic, macrophage, and monocyte cells) and B lymphocytes, but these antigens can be induced on activated T cells and endothelial cells, including the glomerular endothelium, renal tubular cells, and capillaries. The nonclassic class II genes are not expressed on the cell surface but form heterotetrameric complexes involved in peptide exchange and loading onto classic class II molecules. The class III region comprises genes that play in critical immune function such as those encoding tumor necrosis factors, complement proteins, and heat shock proteins.

Structure and Function of HLA Molecules

Although MHC molecules are important barriers to transplantation, their primary function is to provide protection against pathogens. The HLA molecules evolved with an appropriate structure to perform this specialized antigen presentation function in an effective manner. Although class I and class II HLA molecules are encoded by different genes and comprise distinct subunit structures, they are remarkably similar in their three-dimensional crystallographic structures (see front cover).

The class I antigens (HLA-A, -B, and -C) consist of an α heavy chain of 45 kDa with three globular external domains (α1, α2, and α3), a transmembrane region, and an

intracellular domain. The structure is stabilized by a non-MHC encoded β_2-microglobulin (located in chromosome 15) associated with the α3 domain. The class II antigens (HLA-DR, -DQ, and -DP) consist of two noncovalently linked chains: an α-chain of 35 kDa (encoded by DRA, DQA1, or DPA1) and a β chain of 31 kDa (encoded by DRB1, DRB3, DRB4, DRB5, DQB1, or DPB1). Both chains are transmembrane with two globular extracellular domains. The αl and α2 domains of class I molecules fold together into a single structure consisting of two segmented α_1 helices lying on a sheet of eight antiparallel β strands. The folding of the αl and α2 domains creates a long cleft or groove facing away from the cell, in which peptides bind. Similarly, the membrane distal αl and β1 domains of class II molecules form the peptidebinding cleft. The class I and class II molecules differ with regard to the ends of the groove that are closed in class I and open in class II molecules, permitting longer peptides to be accommodated on class II molecules. The HLA antigens (self) with their loaded peptides (nonself) are exposed to T cells, which recognize these compound structures (self + nonself) through their T-cell receptors and trigger immune activation against the foreign antigens (See Chapter 2).

The Nature of HLA Polymorphism

The classic class I and class II genes encode HLA molecules, the most polymorphic proteins known to date in humans. Early studies using serologic typing methods identified an unprecedented number of HLA alleles at each locus. DNA sequencing revealed an even more extensive polymorphism because the serologically defined antigens included multiple allelic variants that could differ by a single nucleotide substitution. The differences among HLA proteins are localized in the antigen-binding domain, particularly enriched in positions that interact with antigenic peptides or the T-cell receptor. Class I polymorphisms are predominantly found in the first 180 amino acids of the heavy chain, and

class II polymorphisms are found in the first 90 to 95 amino acids of the α or β chains, or both. This extreme polymorphism is thought to be driven and maintained by the long-standing battle for supremacy between the immune system and infectious pathogens.

Most amino acid substitutions are shared by more than one HLA molecule and thus demonstrate a patchwork pattern of sequence polymorphism. Antigenic determinants with unique sequence motifs (also called *epitopes*) are known as private specificities. Some antigenic determinants are shared by many HLA antigens. These are called public specificities. The Bw4 and Bw6 specificities are good examples of public antigens. All HLA-B antigens express either Bw4 or Bw6. The antigenic determinant that defines these specificities is affected by amino acids in positions 80 and 83 of the class I molecule sequences located in the exposed part of the α_1 helix. Class I molecules with arginine at position 83 and threonine or isoleucine at position 80 are recognized by anti-Bw4 antisera and include the HLA-B13, -B17, -B27, -B37, -B38, -B44, -B47, -B49, -B51,

-B52, -B53, -B57, -B58, -B59, -B63, and -B77 antigens. The HLA-A23, -A24, -A25, and -A32 antigens also have the characteristic arginine at position 83 and react with anti-Bw4 antibodies. All other B-locus antigens have glycine at position 83 and asparagine at position 80 and react with anti-Bw6 antibodies. A consequence of the patchwork pattern of HLA polymorphism is that an antibody generated against a particular antigen may react to a number of HLA antigens that share the same sequence motifs, a problem referred to as *crossreactivity*. For instance, a patient's serum carrying anti-HLA-A2 antibodies may react to HLA-A2, as well as -A68, -A69, -B57, and -B58, because these antigens share amino acid sequence motifs with HLA-A2.

HLA Nomenclature

One of the most notable features of the HLA system is the remarkable degree of polymorphism exhibited by its gene components. Even when we limit the discussion to the products of the HLA-A, -B, and -DR loci, which are most commonly encountered in clinical kidney transplantation, there are 88 recognized antigens (defined by antibodies), encoded by more than 2200 distinct alleles (Table 3.1), and the number of new alleles is still increasing. Obviously, keeping track of this diversity requires a specialized nomenclature. The HLA antigens were identified and characterized over a 50-year period beginning with the discovery of the MAC (now HLA-A2) antigen by Dausset in Paris in 1958. A series of international workshops, beginning in 1964 and held about every 4 years until 1987, established a nomenclature for the HLA antigens, naming unique antigens in the sequence in which they were officially recognized: Al, A2, A3, Bw4, B5, Bw6, B7, B8, and so on. The antigens were identified using antisera obtained primarily from multiparous women. As the field evolved, new antisera were discovered that could “split” some HLA antigens into narrower specificities. HLA-A9 was split into HLA-A23 and -A24, and HLA-A10 was split into HLA-A25, -A26, -A34, and -A66, for example. Table 3.1 lists the broad parent antigens for splits in parentheses.

The already complicated HLA nomenclature became more complex when DNA-based typing technologies for HLA were developed in the mid-1980s. To accommodate the growing numbers of alleles that could be identified by their unique nucleotide sequences within the antigen designations, the established serologic nomenclature was modified to associate alleles with antigens whenever possible, and four-digit designations were developed in which the antigen designation makes up the first two digits and the sequential allele designation makes up the third and fourth digits. The first allele for HLA-A1 is HLAA*0101, which includes the locus (*A*), an asterisk (*) to indicate the typing was performed by DNA methods, the serologic antigen (*01*), and the allele number

---

(*01*). In cases in which the total number of coding variants exceeds 99, a second number series is used to extend the first one. For example, for the very large B*15 family of alleles, the B*95 series is used to code for additional B*15 alleles. Consequently the next

B*15 allele named following B*1599 was B*9501. Likewise the A*92 series has been used as a second series for the A*02 allele family. The naming of HLA class II antigens is similar, even though two distinct polypeptides encoded by separate genes combine to form the antigen. The DR antigens are distinguished by their DR β_1 subunit; therefore, the first allele of DR1 is DRB1*0101.

TABLE 3.1 Recognized Human Leukocyte Antigen (HLA) Specificities

No. of Alleles	Antigen
HLA-A	
29	A1
134	A2
39	A3
31	A11
19	A23(9)
81	A24(9)

6	A25(10)
35	A26(10)
17	A29(19)
22	A30(19)
21	A31(19)
15	A32(19)
12	A33(19)
8	A34(10)
4	A36
1	A43
7	A66(10)

42	A68(28)
1	A69(28)
12	A74(19)
1	A80
HLA-B	
61	B7
35	B8
20	B13
7	B14
135	B15
27	B18

38	B27
84	B35
13	B37
17	B38(16)
42	B39(16)
78	B40
8	B41
8	B42
58	B44(12)
7	B45(12)

12	B46
5	B47
19	B48
5	B49(21)
3	B50(21)
50	B51(5)
11	B52(5)
14	B53
13	B54(22)
28	B55(22)
21	B56(22)

16	B57(17)
15	B58(17)
2	B59
8	B60(40)
15	B61(40)
24	B62(15)
2	B63(15)
1	B64(14)
1	B65(14)
2	B67

9	B70
3	B71(70)
2	B72(70)
1	B73
5	B75(15)
3	B76(15)
1	B77(15)
5	B78
3	B81
2	B82

HLA-DR

19	DR1
39	DR2
39	DR3
73	DR4
156	DR6
14	DR7
34	DR8
6	DR9
2	DR10
67	DR11(5)
16	DR12(5)

82	DR13(6)
74	DR14(6)
27	DR15(2)
12	DR16(2)
4	DR17(3)
2	DR18(3)
17	DR51
37	DR52
9	DR53

Note: The numbers in parentheses represent prior designations. Data were extracted from the public IMGT/HLA Database (http://www.ebi.ac.uk/imgt/hla).

There are some exceptions that may be confusing. The HLA-B14, -B15, -B40, and -DRB1*03 allele series include distinct antigens that are both immunogenic and antigenic. The HLA-B62 antigen, for example, is encoded by HLAB*1501, 1504, 1505, 1506, 1507, and many other B15 alleles, whereas HLA-B75 is encoded by HLA-B*1502, 1508, 1511, and so on. HLA-DRB1*0301 is HLA-DR17, whereas HLA-DRB1*0302 is HLA-DR18. The correlation between alleles and antigens is updated periodically in the *HLA Dictionary* and in the series “Nomenclature for Factors of the HLA System” (see “Selected Readings”).

Although the number of HLA antigens, alleles, and combinations is very large, the frequencies of individual antigens, alleles, and combinations in a given population vary considerably. The most common HLA antigen is A2, which is found in roughly 50% of individuals from populations around the world. About 96% of whites with European ancestry who express HLA-A2 have the HLA-A*0201 allele. Northern Chinese and many Hispanics who express HLA-A2 have the HLA-A*0206 allele. HLA-B8 is found in 30% of Scots, and the frequency declines as populations in Europe and more distant areas are analyzed, except in those areas that were colonized by the British (South Africa, India, Australia), where the frequency is higher. Thus, certain antigens and alleles are common, whereas others are very rare, and, in fact, no frequencies have been established yet for the majority of alleles because they have not been encountered or detected among donors and recipients. Some HLA antigens are racially limited. Thus, HLA-B54 is found almost exclusively in persons from Japan and nearby Asian countries. HLA-A36 is relatively common among blacks but is very rare in other populations.

The additional HLA polymorphism that has been revealed through the application of DNA technologies has provided interesting insights into the role of HLA in many autoimmune diseases, but its significance in clinical kidney transplantation remains to be seen. Allele differences between the donor and recipient of bone marrow transplants lead to graft-versus-host disease. However, extensive analysis of HLA allele-level mismatches among HLA antigenmatched kidney transplant recipients has revealed no substantial effect of allele-level HLA mismatches on graft survival rates.

Family Segregation of HLA Haplotypes

Each parental chromosome 6 provides a haplotype or linked set of MHC genes to the offspring (Fig. 3.1). Haplotypes are usually inherited intact from each parent, although crossover between the A and B locus occurs in about 2% of offspring, resulting in a recombination (and a new haplotype). The child carries one representative antigen from each of the class I and class II loci of each parent. A child is, by definition, a one-haplotype match to each parent unless recombination has occurred.

HLA haplotypes are inherited in a mendelian fashion. Statistically, there is a 25% chance that siblings share the same haplotypes (two-haplotype match), a 50% chance they share one haplotype (one-haplotype match), and a 25% chance that neither

haplotype is the same (zero-haplotype match). Even in the case of

siblings who share both HLA haplotypes, 25% to 100% of other parental chromosomes may be different, and these other chromosomes include other “minor” histocompatibility antigens, which can also initiate rejection reactions.

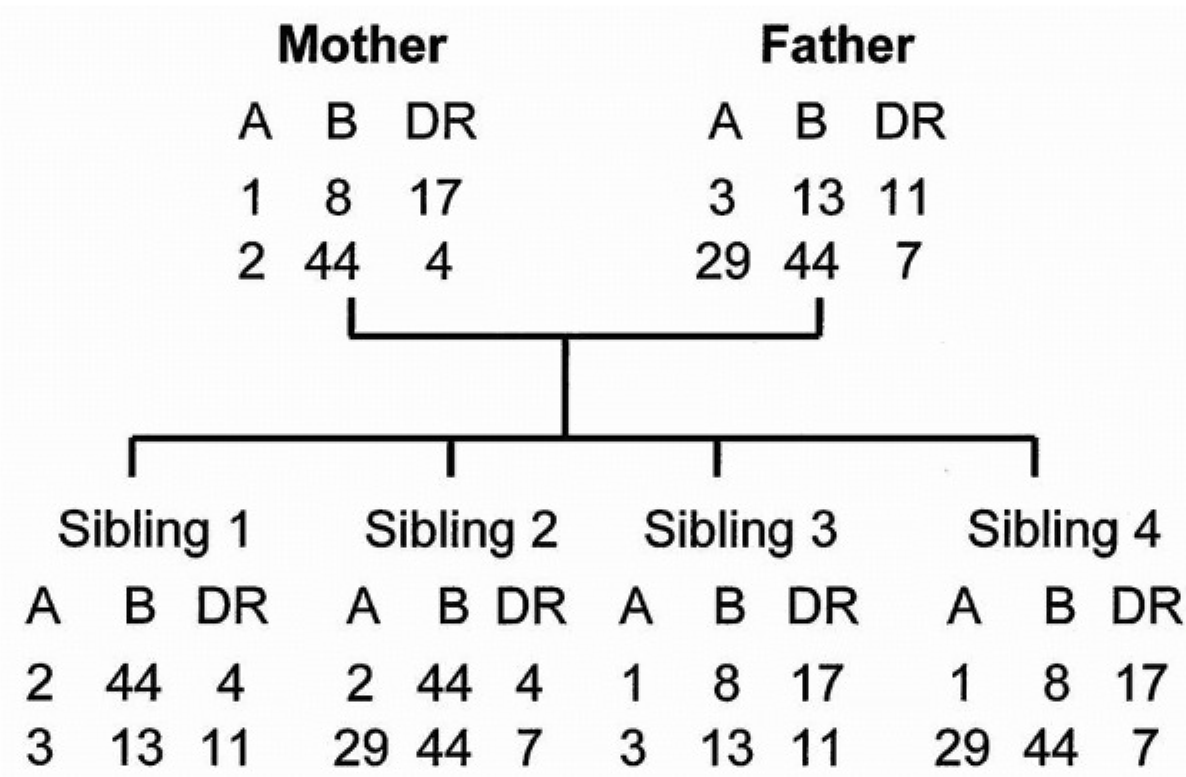


FIGURE 3.1 Inheritance of haplotypes and HLA profile in four theoretical siblings. Sibling 1 is a one-haplotype match to siblings 2 and 3 and a zero-haplotype match to sibling 4.

Definition of Haplotypes and Phenotypes

Consider an individual with the following HLA profile or phenotype: Al, A24, B8, B44, DR4, DR15. From this phenotypic information alone, it is not possible to identify haplotypes because it is not known which antigens are linked on each chromosome. Consider another individual with the following HLA phenotype: Al, A3, B7, B8, DR4, DR12. If this second individual is the biologic parent, offspring, or sibling of the first individual, it becomes possible to identify a shared haplotype of the family as Al, B8, DR4. The first individual also has an unshared haplotype A24, B44, DR15, and the second individual an unshared haplotype A3, B7, DR12. These haplotypes should appear in the parents and other siblings. A kidney transplanted between these two individuals would be a one-haplotype matched graft, and the Al, B8, and DR4 antigens would be genotypically identical in the donor and recipient because they are encoded by the

same inherited genes.

If these two individuals are not related, it is not possible to identify the haplotypes. Thus, in transplants from living unrelated or deceased donors, the haplotypes are unknown, and only the phenotypic identity of individual HLA antigens can be determined. The two individuals whose HLA phenotypes are listed would be called a *three-antigen match* or a *three-antigen mismatch* (see "HLA Matches and Mismatches"). Sharing of minor histocompatibility antigens is serendipitous.

Linkage Disequilibrium

Although it is not possible to identify an individual's haplotypes from the phenotypic HLA typing information alone, within racial or ethnic populations, certain HLA determinants are inherited together more often than would be expected by chance. For example, if HLA-A1 and HLA-B8 occur at gene frequencies of 16% and 10%, respectively, in a population, the probability of finding them together should be 1.6%. However, the actual occurrence rate of the HLA-A1-B8 combination is significantly above the predicted incidence (about 8%). This phenomenon represents the inheritance of haplotypes within racial groups. Existing data suggest that positive selection is operating on the haplotype and that the linked loci confer a particular selective advantage for the host.

HLA Matches and Mismatches

It is not always possible to identify two HLA specificities at each HLA locus. Consider the HLA phenotypes for the following two unrelated individuals:

1. A2, —; B27, B13; DR17, DR4
2. A2, A3; B8, B14; DR17, —

The absence of the second A-locus antigen in individual 1 and the second DR-locus antigen in individual 2 could result from a failure to identify the second antigen. More often, it reflects the inheritance of the same antigen (A2 and DR17 in these cases) from both parents (the individuals are homozygous at these loci). Among whites, the latter is usually the case. A kidney transplanted between these two individuals would be described as a one A and one DR match, but this terminology does not take into account homozygosity in the A and DR loci of individuals 1 and 2, respectively. If individual 1 were a donor for individual 2, it would be more informative to describe the combination as a zero A, two B, and one DR mismatch. If individual 2 were a donor for individual 1, the combination would be a one A, two B, and zero DR mismatch. Antigenic differences in the donor kidney are potential targets of rejection; therefore, the convention of counting the number of donor HLA antigens that are *not* shared by the recipient provides an estimate of the antigen dose.

Identical and Fraternal Twins

The differentiation between identical twins and two-haplotype-matched fraternal twins is important because the recipient of a transplant from an identical twin requires no immunosuppression. The procedure is immunologically equivalent to an autotransplantation. Two-haplotype-matched siblings, whether they are fraternal twins or not, differ in their minor histocompatibility antigens, and immunosuppression is required. Monozygotic, or identical, twins share a single placenta and amniotic sac at birth. However, such information may be unavailable or unreliable when the patient and donor are evaluated as adults. A variety of methods have been used to identify monozygotic twins, including skin grafting from the potential twin donor to the recipient (the graft would be rejected if the twins were fraternal). Today, several genetic polymorphisms can be exploited to determine identity at many genetic loci, providing a high degree of confidence that twins are identical. Extended blood groups include markers that are determined by many genes on different chromosomes. Analysis of short tandem repeats (STRs), which, as the name implies, are short nucleotide sequences that are repeated a variable number of times, provide a high probability of identifying differences between individuals. STRs are often used in monitoring engraftment of HLA-identical bone marrow transplants, so they are exquisite markers of individuality.

HLA TYPING TECHNIQUES

The Microcytotoxicity Test

The microcytotoxicity test developed by Terasaki and McClelland in 1964 was the international standard test for HLA typing for more than 30 years. This serologic test is performed in small plastic trays with a grid of small flatbottomed wells, each of which contains 1 μL of a selected antiserum suspended

---

in 5 μL of mineral oil to prevent drying. One microliter of a lymphocyte suspension (at a concentration of 2×10^5/mL) from the individual to be typed is added to each well, mixed, and incubated. Complement is added, and after another incubation, a vital dye is added to indicate the proportion of dead cells in each well when examined under the microscope. Using the products of an immune response (antibodies) to measure the targets of an immune response (HLA antigens) has a certain inherent logic. If an antigen had provoked an antibody response, its immunologic importance was demonstrated. However, the HLA-typing antisera are seldom monospecific (i.e., they do not recognize a single private specificity), so in most cases, it is necessary to examine the patterns of reactivity with several antibodies to determine the HLA type.

DNA Typing Methods

It is now more common to type individuals by DNA-based rather than serologic methods. Using the extensive DNA sequence data available, oligonucleotide primers and probes that specifically hybridize to sites that are unique to an HLA locus, allele, or group of alleles have been developed and are commercially available for HLA typing. Three basic methods used in conjunction with polymerase chain reaction (PCR) employ sequence-specific oligonucleotide probes (SSOPs), sequence-specific primers (SSPs), and sequencing-based typing (SBT). SSOP is based on first amplifying genomic DNA using locus- or group-specific primers and then detecting the hybridization of specific oligonucleotide probes tagged with enzymatic or fluorescent markers to the amplified product. In commercial kits, the process is often reversed, with the probes attached to mylar strips or to microparticles that can be hybridized with the labeled PCR product to produce a series of colored bands or fluorescent beads when hybridization occurs. The developed strips can be read manually or scanned, and the microparticles read on a flow cytometer. SSP depends on DNA amplification using group- or allele-specific primers and detecting an amplified product of the correct size by gel electrophoresis. The size is determined by running an agarose gel that separates the PCR products according to their size. SBT uses gene-specific primers to sequence polymorphic regions of the gene, and alleles can be assigned based on the nucleotides identified at key positions in the sequence. Even with these molecular approaches to HLA typing, it is difficult to produce reagents that uniquely recognize each individual HLA antigen. As with serology, it is often necessary to identify patterns of primer and probe reactivity in order to determine the HLA type. Computer programs assist in the analysis of primer and probe patterns, which are more difficult to analyze unaided because of the added complexity of the HLA genes. It is difficult to identify HLA alleles without performing sequence-based typing because the differences between alleles may be determined by single nucleotide differences. However, SSP and SSOP can easily provide low or intermediate levels of typing, identifying the recognized HLA antigens and major allele groups, respectively. This level of typing is sufficient for renal transplantation in most cases.

DNA-based typing offers several advantages over serology, including greater accuracy and reproducibility of the reagents. Viable lymphocytes are not required. Typing can be performed on any tissue containing nucleated cells. Buccal swabs can provide sufficient DNA for tissue typing and may be preferable to drawing blood from infants or from those who are squeamish about needles. Samples can be dried on filter paper and stored without refrigeration for extended periods. The oligonucleotide reagents are more easily standardized and controlled, and they can be synthesized when needed. The accuracy of DNA typing is better than has been achieved using serology. The more difficult HLA specificities, those for which highly specific alloantiserum is rare or not widely available, can be accurately identified using DNA testing. For example, HLA-DR6 and its splits, -DR13 and -DR14, had been troublesome for many years because antisera could not be obtained. It is now known that HLA-DR6 is composed of at least 156 alleles

of HLA-DR13 and -DR14. Laboratories around the world generally have been successful in typing the DR13 and DR14 splits of DR6 by using DNA typing. For the most part, the concordance of DNA and serologic typing for HLA has been high for the broad specificities, but DNA is clearly the superior method.

ANTI-HUMAN LEUKOCYTE ANTIGEN ANTIBODIES

Patients who have circulating anti-HLA antibodies are at high risk for hyperacute rejection (the immediate and sometimes irreversible destruction of the transplanted kidney) or of accelerated acute rejection (an early and rapid antibody-mediated rejection) (see Chapters 9 and 24). The presence of preformed anti-HLA antibodies restricts the number of compatible donors for the sensitized patient to those who do not express the HLA antigens to which the patient is sensitized. Sensitized patients often must wait substantially longer for a crossmatch-compatible kidney. Evaluation of HLA antibodies in the serum of a transplantation candidate is the transplant equivalent of ABO blood group typing for a blood transfusion. The consequence of proceeding with transplantation or transfusion with the presence of reactive antibody is similar. The former produces red blood cell lysis and a transfusion reaction, and the latter results in hyperacute rejection. Assiduous attention to pretransplantation lymphocyte crossmatching has virtually eliminated hyperacute rejection as a clinical threat.

Origins of Alloantibodies

During pregnancy, the semi-allogeneic fetus develops and is tolerated within the mother for 9 months. At birth and during the pregnancy, the mother is exposed to paternal HLA antigens of the fetus and may become immunized and produce anti-HLA antibodies to the mismatched HLA antigens derived from the father. Sera from multiparous women were collected and screened against large panels of lymphocytes to identify HLA-typing reagents for the microcytotoxicity test. Among patients awaiting kidney transplantation, sensitization occurs in up to 25% of women with a history of pregnancy and is usually highest in those with multiple pregnancies. Exposure to allogeneic HLA antigens also occurs following blood or platelet transfusion and loss of an organ transplant, and anti-HLA antibodies can develop as a result of viral or bacterial infections.

The specificity of anti-HLA antibodies an individual produces on exposure to allogeneic HLA molecules is influenced by the individual's immunologic history and by the individual's own HLA type. Antibodies are generally not produced against self HLA antigens. Anti-HLA antibodies can be directed against private specificities such as HLA-A1, or against public specificities such as Bw6. Antibodies to private specificities recognize an epitope that is unique to a particular HLA molecule or a limited group or family of closely related alleles, whereas antibodies to public specificities recognize an epitope that is shared by more than one HLA molecule. Public epitopes are responsible for cross-reactivity observed in HLA alloantiserum. HLA antigens that share epitopes

can be grouped into the major cross-reactive groups (CREGs) listed in Table 3.2.

Measurement of Anti-Human Leukocyte Antigen Antibodies

When the first crossmatch results were reported by Patel and Terasaki in 1968 and showed that among 30 patients transplanted with a positive cytotoxicity crossmatch, 24 suffered hyperacute rejection and three others lost their grafts within the first 3 months, the authors also reported that patients could be screened beforehand against a panel of normal individuals representative of the local donor pool. Patients who had no positive tests against the panel had a very low incidence of hyperacute rejection. Thus, patients could be screened in advance of a final crossmatch to determine whether they had antibodies against a panel of donors, and the result would provide an estimate of how often the patient would have a positive crossmatch against donors who became available.

TABLE 3.2 HLA Antigen Cross-Reactive Groups (CREGs)

A1C	A1 3 11 29 30 31 32 36 74 80
A2C1	A2 B17 57 58
A10C	A10 19 25 2629 30 31 32 33 34 66 74
A9C	A2 9 23 24 28 68 69
A28C	A2 28 68 69
B5C	B5 18 35 37 51 52 53 58 78

B7C	B7 8 13 40 41 42 48 60 61 81
B8C	B8 14 16 18 38 39 64 65
B12C	B12 13 21 37 40 44 45 47 49 50 60 61
B21C	B5 15 17 21 49 50 51 52 53 57 58 62 63 70 71 72 73 75 76 77 78
B22C	B7 22 27 42 46 54 55 56 73 81 82
B27C	B7 13 27 40 41 42 47 60 61
Bw4	A9 23 24 25 32 B5 13 16 17 27 37 38 44 47 49 51 52 53 57 58 59 63 77
Bw6	B7 8 14 18 22 35 39 40 41 42 45 46 47 48 50 54 55 56 60 61 62 64 65 67 70 71 72 73 75 76 78 81

The screening process must ensure a true negative crossmatch with the intended donor by accounting for all relevant antibodies and avoiding a false-positive crossmatch with clinically irrelevant antibodies. Information from anti-HLA antibody testing is used to (1) predict the likelihood of finding a crossmatch-compatible donor; (2) avoid transplantation with a donor carrying HLA antigens to which the patient is sensitized; and (3) avoid a false-positive crossmatch with a donor by excluding clinically irrelevant antibodies. The methods for detecting and characterizing anti-HLA antibodies have evolved during the past 40 years.

Cytotoxicity

Until recently, the complement-dependent lymphocytotoxicity (CDC) assay was the most common method for anti-HLA antibody screening. The patient's serum is incubated separately with B cells and T cells from panels of donors selected to represent the known HLA class I and class II antigens, respectively. Complement is added and cell lysis detected, as noted previously for the microcytotoxicity test. Prolonging the complement incubation time increases the sensitivity of the test and enhances the detection of low-titer antibodies. The results are usually expressed as the percentage of panel cells that are killed by the serum. The anti-HLA antibodies that are detected are called panel-reactive antibodies (PRAs). Thus, on a 50-cell panel, a positive reaction against 30 donors represents a PRA of 60%.

IgG antibodies reactive to HLA class I antigens (found on both T and B cells) are the most important. These antibodies react with T cells at 37°C (98.6°F) (and are sometimes called *T warm antibodies*). The importance of anti-DR and anti-DQ antibodies (reactive to B cells) remained unclear for a long

---

time. However, now there is a large body of evidence showing that both antibodies directed against HLA class I and class II antigens pose significant risks to transplantation outcome. There are several reports of hyperacute and accelerated rejection caused by anti-DR or anti-DQ antibodies.

IgM antibody is characterized by reactivity at 4°C (39.2°F), and its activity can be removed by heating the serum to 55°C (131°F) or by treatment with a reducing agent, such as dithiothreitol (DTT). IgM antibody is often autoantibody and is commonly detected in the sera of patients with autoimmune disorders such as systemic lupus erythematosus. IgM antibodies can usually be ignored.

Anti-Human Globulin-Enhanced Cytotoxicity

The CDC assay typically detects high-affinity antibodies that efficiently activate complement. Many of the public antibodies that are often present in the sera of highly sensitized patients cannot be detected by the standard CDC assay. Antibodies to CREGs often exhibit a cytotoxicity-negative, adsorption-positive reactivity as they bind to lymphocytes, but do not always fix complement and hence are not cytotoxic. Many anti-CREG antibodies appear to react with a private HLA specificity when tested in a standard cytotoxicity assay. However, when tested with more sensitive techniques, such as anti-human globulin (anti-HG)-enhanced cytotoxicity, flow cytometry, or solid-phase assays, reactivity toward the associated CREG specificity becomes apparent.

The cytotoxicity test can be enhanced by adding anti-HG to the microcytotoxicity plate after adding the patient's serum and before addition of complement. Anti-HG promotes complement fixation by cross-linking bound HLA antibody. The anti-HG test is more sensitive than the standard CDC test and detects lower titer and noncytotoxic

antibodies. The anti-HG reagent must be standardized using sera known to have noncytotoxic anti-HLA antibodies because its titer and specificity may vary.

Flow Cytometry

Flow cytometry is an even more sensitive antibody assay. To determine PRA, a mixture of target cells composed of lymphocytes from 5 to 10 donors is used. Target cell mixtures are selected to represent CREGs and DR antigens. The patient's serum is mixed with target cells; the cells are washed and then incubated with monoclonal mouse anti-CD3 (a pan T-cell marker) and anti-CD19 or anti-CD20 (both B-cell markers) antibodies conjugated with fluorescent dyes such as phycoerythrin or PerCP, respectively, and an anti-human IgG antibody conjugated with fluorescein. The T cells that stain red-orange and the B cells that stain red can be gated using a flow cytometer, making the amount of yellow-green fluorescence proportional to the concentration of anti-T-cell or antiB-cell antibodies present in the serum.

Solid-Phase Assays

Solid-phase assays using affinity-purified HLA antigens are now available on a variety of platforms. These currently fall into one of three main groups: a mixture of affinity-purified HLA class I or class II antigens used to screen for the presence or absence of anti-HLA antibodies, affinity-purified class I or class II antigens from individual donors used like donor cell panels to assess reactivity with individual donor phenotypes, but with the advantage of a clear separation of class I and class II phenotypes, and recombinant single HLA antigens attached to solid supports, permitting a precise specificity determination. The most versatile platform uses microparticles or beads coated with purified HLA class I or class II antigens as antibody targets. The microparticles are colored to permit discrimination of a large number (more than 100) of beads

---

simultaneously, each with distinct, chemically attached HLA antigens. Patient serum is incubated with a mixture of beads, washed and bound antibody is detected by adding fluorescently labeled anti-human IgG and measuring fluorescence in a flow cytometer or similar device. Interpretation of the test results is based on comparisons of fluorescence intensity measurements of the test serum to those of positive and negative serum controls. Neither viable lymphocytes nor complement fixation is required, and the assays are robust. The presence or absence of anti-HLA antibodies can be readily detected using pooled soluble antigens, which is a low cost, rapid assay for the detection of antibody. Targeted HLA specificities can further be determined using a panel of HLA antigens from individual donors or by using single HLA antigens.

Determination of the Specificity of Anti-Human Leukocyte Antigen Antibodies

It is often possible to determine the HLA target specificities (a list of HLA antigens that react with the patient's serum) by analyzing reaction patterns against the HLA types of the panel donors. Determination of antibody specificity is based on a statistically significant correlation between the pattern of serum reactivity and the pattern of a particular HLA antigen in the panel. Precise definition of antibody specificity may be affected by the presence of multiple antibodies or the panel size and composition of the panel phenotypes. When multiple antibodies are present in a serum, antibodies to more frequent HLA antigens may mask the recognition of antibodies to less frequent antigens. The problem is reduced by using large panels of target cells or by using singleantigen beads with recombinant HLA antigens. The introduction of solid-phase technologies for measuring anti-HLA antibodies represents a major change in the sensitivity and precision of antibody identification for laboratories. Single antigen beads can precisely identify individual HLA antigen reactivities, even in a complex serum containing antibodies that could not be resolved using cells or beads with multiple HLA antigens attached.

Unacceptable Antigens

When a patient has well-defined anti-HLA antibodies that would result in a positive crossmatch against donors who express the target HLA specificities, the United Network for Organ Sharing (UNOS) permits the inclusion of those HLA antigens to avoid (unacceptable) as part of the patient's waitlist profile. If a patient has a clearly defined antibody to HLA-A1, potential donors expressing HLA-A1 would not be acceptable, and kidneys from these donors will not be offered to that patient, thus avoiding a predictably positive crossmatch. Most transplantation centers would not transplant in the face of a positive CDC or anti-HG crossmatch because of the high risk for hyperacute rejection. However, the results of transplantation with lower levels of antibodies may be beneficial for the patient despite the anticipation that antibodies cause a higher incidence of delayed graft function, accelerated humoral rejection, and chronic allograft dysfunction. Thus, transplantation centers may differ in their preference for listing unacceptable antigens that would not result in a positive CDC or anti-HG crossmatch but that might cause a positive crossmatch using flow cytometry or another very sensitive crossmatch test.

The solid-phase tests for defining anti-HLA antibody specificity are exquisitely sensitive and may detect antibodies that are present at very low levels that may not damage the graft. Testing sera at multiple dilutions shows that the degree of fluorescence shift is proportional to the titer of antibody, and this is important in determining which donor HLA antigens should be avoided to prevent hyperacute, accelerated acute antibody-mediated rejections or chronic graft damage. Laboratories are working diligently to relate the strength of

---

reactions to antibody levels that might lead to patently adverse outcomes. Of course, the patient's immunologic history also plays a role in assessing the risk for low-level

antibodies. A patient with a prior graft loss or multiple pregnancies may have developed memory to mismatched HLA antigens, and weak antibodies may represent the potential for a rapid increase in antibody levels after transplantation with previously mismatched HLA epitopes. Laboratories must now identify donor HLA antigens that their transplantation centers would consider unacceptable for a sensitized patient because of the presence of specific anti-HLA antibodies identified by any means provided at least one solid-phase test was used. The unacceptable antigens are determined by practices at each individual transplantation center and might also include antigens that were mismatched in a previous failed transplantation.

Calculated Panel-Reactive Antibodies

The PRA, which initially predicted the percentage of crossmatch incompatible local donors, evolved from its original form to a less meaningful measure of sensitization with the introduction of more sensitive antibody tests and developments in our understanding of HLA antigens. When the PRA test was first developed, only a few class I HLA antigens had been characterized. As more HLA antigens were identified, the panel compositions were adjusted to include as many different antigens as possible, which meant that common HLA antigens, such as A2, were underrepresented, and rare antigens were overrepresented on the panels. Although these changes improved the chances of detecting HLA antibodies directed against any of a broad spectrum of HLA antigens, the correlation between PRA and probability of a positive crossmatch against potential donors was lost because the frequencies of antigens on the panel had been altered. The recognition of HLA class II (HLA-DR, -DQ) antigens in the 1970s added another level of complexity to the measurement of PRA. The class II antigens are expressed on B but not T lymphocytes, so laboratories began to screen B and T cells separately to identify antibodies against class II antigens. This approach yielded two PRA values, one for the T-cell panel and a second for the B-cell panel. The panels, which often differed to ensure representation of class II antigens independently of class I and T-cell panels, measured antibodies against class I only, whereas B-cell panels detected antibodies against both class I and class II antigens.

The use of lymphocytes as antibody targets permitted an indirect way to identify specific anti-HLA antibodies in the serum. The antibody specificities could be deduced from reaction patterns against cell panels with defined HLA types, but their usefulness in characterizing broadly reacting antibodies was limited by the fact that HLA antigens were often “masked” by others that were expressed on the same cells, as noted previously. It was also difficult to discriminate between antibodies against HLA class I and class II with confidence because both are expressed on B lymphocytes.

Although solid-phase tests now permit a sensitive, precise, and reproducible determination of a patient's circulating anti-HLA antibodies, they still do not provide what was the key component of the PRA, an estimate of the percentage of crossmatch-incompatible donors. This is important because broadly sensitized patients (currently

those with 80% or more PRA) are awarded points in the kidney allocation scheme to compensate for their disadvantage caused by the fact that most donors are not crossmatch compatible.

UNOS implemented a new policy in December 2007 designed to address the variability in PRA reporting that had developed over the years through the use of different cell panels and different tests for anti-HLA antibodies. The calculated PRA (CPRA) is calculated by determining the frequency of incompatible donor HLA phenotypes based on the unacceptable class I and class II HLA

---

antigens that have been listed for each candidate. Because the HLA-A, -B, -Cw, -DR and -DQ types of actual deceased kidney donors were used to compute the frequencies, the CPRA reflects the true probability of an incompatible donor based on the unacceptable antigens that have been listed for a patient. A CPRA of 80% means that 80% of deceased donor kidneys are not acceptable and will not be offered to that patient. Although we might anticipate that different regions might have different HLA antigen distributions because they differ in the racial and ethnic populations, preliminary studies suggest that these variations do not result in substantially different CPRAs.

Pretransplantation Crossmatch

The crossmatch test is the final pretransplantation immunologic screening step. Using the previously described HLA antibody screening assays, the potential donor's lymphocytes serve as the target cells for the patient's serum. The presence of cytotoxic IgG antidonor HLA antibodies is a strong contraindication to transplantation. Most transplantation centers use the more sensitive anti-HG augmentation or flow cytometry, in addition to the cytotoxicity test, to detect even low levels of antibody. Enzyme-linked immunosorbent assay (ELISA) tests using isolating donor antigens have yet to gain widespread acceptance.

Preliminary Crossmatch

Patients with high PRA have accumulated on waiting lists because of the difficulty in finding suitable crossmatch-negative donors. To expedite the crossmatch procedure, screening tray sets with recent serum samples from sensitized patients are prepared either quarterly or monthly. Separate tray sets are made for patients with blood groups A or AB, B, and O, and a “preliminary” crossmatch is performed by testing donor cells on the appropriate tray set at the time of donor HLA typing. Sensitized patients with a positive crossmatch are excluded, but those with a negative preliminary crossmatch and 80% or more PRA receive special consideration in the ranking of candidates. When the preliminary crossmatch is negative, a final crossmatch using either anti-HG or flow cytometry is performed with recent or fresh sera.

Many laboratories now perform a “virtual” preliminary crossmatch. When a candidate's unacceptable antigens have been properly identified and entered into the UNOS

database (UNET) system, the unacceptable antigens predict which donors will have a positive crossmatch. Because UNOS does not offer kidneys from donors with a predicted positive crossmatch to a candidate, the preliminary crossmatch is performed by the computer. Ultimately, virtual crossmatches may replace the need for a final crossmatch as well, permitting shipment of organs for sensitized patients based on a predicted negative crossmatch.

Final Crossmatch

When sera from waiting patients are collected monthly and are available in the laboratory, a final crossmatch can usually be performed without obtaining a fresh sample from the patient. This allows the laboratory to perform final crossmatches for a deceased donor kidney before organ procurement in most cases, avoiding delays in transplantation. Some centers allow older sera to be used if the patient is not sensitized and has not received a recent blood transfusion.

IgM autoantibodies can cause false-positive lymphocytotoxic crossmatch test results. The most straightforward approach to detecting autoantibodies is the auto-crossmatch. Adsorption of the antibody on autologous cells can remove the antibody and render the serum negative. Alternatively, DTT is used to eliminate IgM autoantibodies. If the serum contains a mixture of autoantibodies and alloantibodies of the IgG isotypes, auto-adsorption would be required to remove the autoantibody and leave behind the alloantibody. When the autoantibody is of the IgM isotype, the IgG alloantibody would remain even after DTT treatment. A serum that reacts with lymphocytes, but not with purified HLA class I or class II antigens (as detected by flow cytometry or ELISA), is also suggestive of autoantibodies. Sera from patients with demonstrated IgM autoantibodies should be heated or treated with DTT to eliminate IgM before the final crossmatch to avoid a false-positive result. Not all IgM antibodies are benign. IgM antibodies with anti-HLA specificity are associated with hyperacute or accelerated rejections in isolated cases. Thus, the patient's antibody profile should be thoroughly evaluated before transplantation. When testing is performed by flow cytometry, the specificity of the second antibody can be used to determine the antibody class. Typically, these tests employ anti-human IgG antibody; therefore, IgM reactions are not detected.

Flow Cytometry Crossmatch. The flow cytometry crossmatch (FCXM) test is a very sensitive crossmatch test. Although a positive lymphocytotoxic crossmatch is a contraindication to kidney transplantation, the place of the flow cytometry crossmatch is still somewhat controversial. The test can detect very low levels of circulating antibodies. Positive flow cytometry crossmatches are associated with a higher rate of early acute rejection episodes and a lower 1-year graft survival rate. Hyperacute rejection has not been reported, however, and some transplants across a positive FCXM have no early problems (if the cytotoxic crossmatch is negative). The T-cell FCXM is

particularly useful for sensitized and retransplantation candidates whose antibody levels may have fallen but who can mount a rapid memory response on challenge. Low levels of circulating antibody have a more profound effect when the deceased donor is older or the kidney quality is uncertain. The potential for false-positive reactions is responsible for much of the uncertainty about the role of the flow cytometry crossmatch. Positive, particularly weakly positive, flow crossmatch results should be supported by the patient's sensitization history or be consistent with a determination that the patient has anti-HLA antibodies based on the results of solid-phase assays. When the flow crossmatch detects antidonor HLA antibodies, there is a substantial risk for adverse outcomes after transplantation.

Pronase Treatment of Donor Cells. False-positive FCXMs are often caused by nonspecific immunoglobulin binding to immunoglobulin Fc receptors on lymphocytes, and the degree of binding may vary among individual donors. Patients who have been treated with antibodies such as rituximab (anti-CD20 antibody) may also have false-positive FCXM results owing to the presence of the administered antibody in their serum. Pronase is a nonspecific peptidase that preferentially digests Fc receptors and other cell surface proteins without substantially destroying HLA molecules under certain conditions. Pretreating donor lymphocytes with pronase reduces nonspecific binding of patient serum to lymphocytes and reduces the incidence of false-positive reactions in the FCXM. Caution is required, however, because prolonged treatment or too much enzyme results in loss of HLA antigens. Even under optimal conditions, many cells and nuclei may be lysed during treatment, releasing DNA, which causes clumping and loss of cells. This can be avoided by including DNAase in the treatment.

Desensitization of the Sensitized Patient

More than 25% of renal transplantation candidates are highly sensitized. Two approaches based on the use of intravenous immune globulin (IVIG) are

---

currently used to reduce HLA allosensitization and facilitate transplantation of highly sensitized patients. The first therapy is based on infusion of high-dose IVIG, a second approach uses a combined regimen of cytomegalovirus (CMV)IVIG therapy and plasmapheresis (see Chapter 5 and Tables 5.4 and 5.5). Plasmapheresis rapidly depletes donor-specific antibody, and administration of CMV-IVIG blocks resynthesis of anti-HLA antibodies. Treatment is continued until donor-specific anti-HLA antibodies are no longer detected in the patient's serum. Treatment with CMV-IVIG and plasmapheresis is also effective in reducing HLA allosensitization in highly sensitized patients and is a successful therapy for the treatment of humoral rejection. Combined plasmapheresis and IVIG is also reportedly effective in removing anti-A or anti-B isoagglutinins before successful transplantation across ABO blood group barriers. The precise immunomodulatory mechanisms of the combined therapy are unknown but appear to function in a long-term, donor-specific manner.

IMMUNOLOGIC EVALUATION OF TRANSPLANTATION CANDIDATES

Candidates for renal transplantation today fall into one of two categories: those with a potential living donor and those without. Figure 3.2 outlines the initial immunologic evaluation of these candidates. Once a patient is identified as a suitable candidate for transplantation, HLA typing and antibody-screening tests are performed using the tests outlined previously. The HLA type permits assessment of donor and potential recipient pairs for degree of histocompatibility as well as evaluation of sensitization and crossmatch results. In the case of sibling donors, the HLA-identical sibling kidney provides superior long-term graft survival, and less immunosuppression is needed. The HLA-A, -B, and -DR types are required to list a patient as a candidate for a deceased donor kidney with UNOS. The sensitization status of the patient is also determined before transplantation to identify patients who are at risk for hyperacute or accelerated acute rejection. The patient's PRA level is another important element in listing a renal candidate with UNOS because patients with a PRA greater than 20% receive special ranking in organ allocation. A panel screening by cytotoxicity should be followed by a more sensitive test to identify unsensitized patients. Autoantibodies and other antibodies that do not pose a significant risk for hyperacute or accelerated rejection should be identified before transplantation, and for those without a living donor, these antibodies should be characterized before a deceased donor kidney is offered. Thus, patients with IgM antibodies should be identified and retested after reduction. When the PRA is less than 75%, there is a reasonable chance that specific antibodies can be identified either through analysis of the panel types or by using a microparticle test with coupled HLA antigens. For patients who will wait for a deceased donor kidney or when the living donor transplant will be delayed, it is necessary to monitor changes in patterns of sensitization and reevaluate patients periodically to keep abreast of their current sensitization status.

Patients with a suitable living donor can proceed to a preliminary crossmatch against their donors and, if negative, can undergo transplantation. When there are multiple potential donors, the evaluation of each donor can be tailored to determine whether antibodies are directed against the specific mismatched donor HLA antigens and whether desensitization procedures could permit successful transplantation with one or more potential donors. For patients without a living donor, it is important to investigate and characterize sensitization early in the process, before a deceased donor kidney is offered.

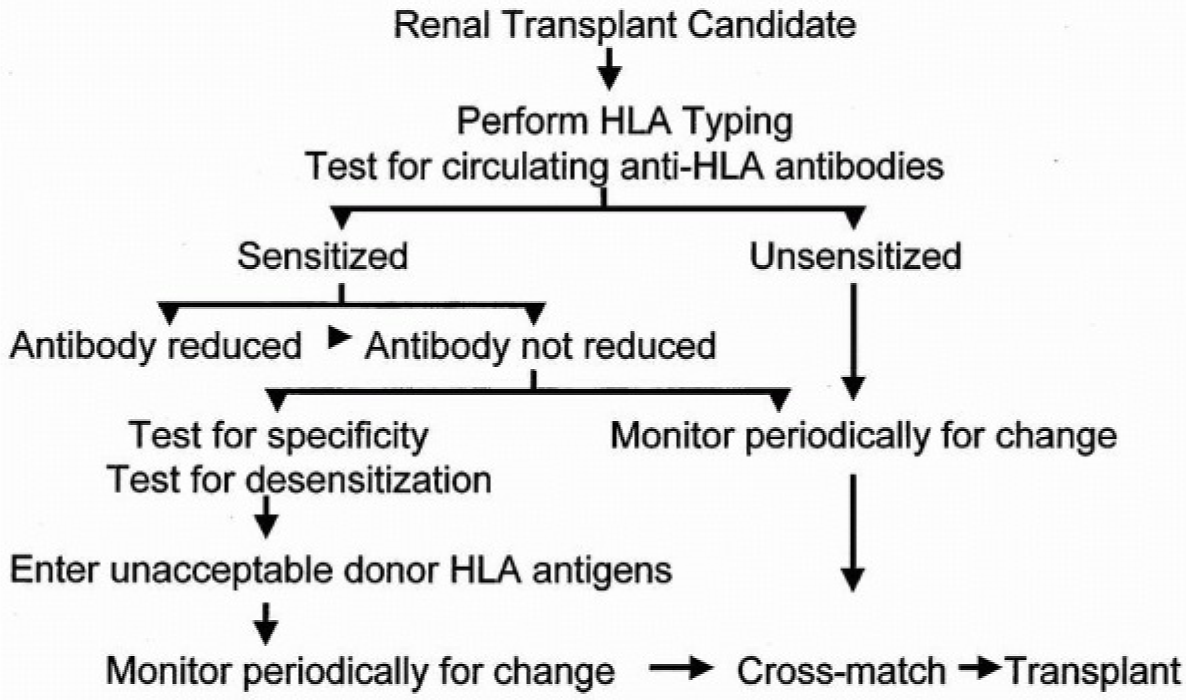


FIGURE 3.2 Strategy for immune monitoring of patients waiting for transplantation.

THE ROLE OF ABO BLOOD GROUPS IN TRANSPLANTATION

The ABO blood group antigens behave as strong transplantation antigens, and transplantation across ABO barriers usually leads to irreversible hyperacute rejection. In principle, the same criteria determine kidney distribution according to ABO, as do blood transfusions with group O (the universal donor) and group AB (the universal recipient). The disproportionate percentage of waiting patients who are type O or type B generally mandates that blood group identity rather than blood group compatibility determine the distribution of deceased donor kidneys. Exceptions are made for blood group AB patients who may be offered A or AB kidneys, and for zero-HLA antigen-mismatched kidneys, which can be offered to an ABO-compatible recipient if an ABO-identical recipient is not available. For living related donor transplantation, ABO compatibility is adequate.

Attempts have been made to overcome blood group barriers when there is a willing ABO-incompatible living donor by removing blood group isoagglutinins with plasmapheresis or immunoabsorption, often in conjunction with splenectomy. ABO-incompatible transplantations have now been performed successfully at many centers, with the largest experience in Japan and Korea, where deceased donor transplantation is not well established (see Chapter 6). Exchange programs are also being tested at several transplantation programs, allowing paired exchanges between unrelated individuals who are both incompatible with their intended recipients but reciprocally

compatible with the patient from the other pair (see Chapter 6).

In white populations, about 20% of blood group A individuals can be defined as A_2; these patients have reduced levels of A antigen on graft endothelium. They may permit an exception to the ABO-incompatibility barrier because A_2 kidneys can be safely transplanted into O or B recipients with low preoperative titers of isoagglutinin. Transplantation of A_2 kidneys into O or B recipients is routine in some centers.

Table 3.3 lists the distribution of the major ABO groups among deceased donors and different ethnic groups of potential kidney transplant recipients. If all ethnic groups contributed equally to the donor pool and all ethnic groups suffered end-stage renal disease in direct proportion to their representation in the general population, waiting times for the different ethnic groups and blood

---

group categories would be the same. In fact, whites contribute disproportionately to the donor pool and blacks contribute disproportionately to the recipient pool because kidney disease is more common in blacks. As a result, patients with blood group O or B wait longer for a blood group-identical donor.

TABLE 3.3 Percent Distribution of ABO Blood Groups Among Kidney Donors in 2007 and According to Ethnicity on the Transplantation Waiting List

Blood Group	Donors	White	Black	Asian	Waiting List*
O	49	49	52	41	52
A	36	36	23	23	29
B	12	12	21	30	16
AB	4	3	3	5	3

n	7,241	29,212	25,950	4,983	74,746

* The waiting list, including all ethnicities and donor ABO types, was compiled by the United Network for Organ Sharing research department as of March 7, 2008.

ROLE OF HUMAN LEUKOCYTE ANTIGEN MATCHING IN TRANSPLANTATION

The HLA antigens are strong transplant antigens that may engage large numbers of T cells (estimates of up to 100 times as many T cells as nominal protein antigens have been reported). Secondary cellular or humoral immune responses to HLA antigens may occur as a consequence of prior exposures to allogeneic HLA through pregnancy, blood transfusion, or previous transplantation. Studies have consistently shown a stepwise increase in early rejections and a decrease in long-term graft survival with increasing numbers of HLA antigen mismatches between the deceased donor and recipient. Paired kidney studies also show that when one kidney is transplanted to an HLA-matched recipient, even if it has been shipped a great distance, and the other is transplanted locally to an HLA-mismatched recipient, the HLA-matched kidney has better long-term graft survival.

Recognition of the special immunologic status of HLA-matched transplants led to the development of a national organ distribution for the sharing of donor kidneys for HLA-matched recipients. Initially, mandatory sharing was limited to patients who matched the donor at all six HLA-A, -B, and -DR antigens. Only about 3% of patients received a six-antigen-matched graft under these stringent criteria. The rules were relaxed in 1990 to allow sharing for homozygous donors and recipients, and again in 1995 to allow sharing when the donor had no HLA antigens that were not in common with the recipient. The proportion of HLA-matched transplants increased to about 8% after 1990 and to 15% after 1995 with the relaxed criteria. To achieve this level of matching, each donor's HLA type is compared with those of all waiting patients in the United States.

As the number of expanded criteria donors has increased, however, the utility of HLA matching as a kidney allocation strategy has become more complex. Although HLA-matched kidneys have better survival rates than comparable mismatched kidneys, the survival difference between expanded criteria donor kidneys and standard criteria kidneys is even larger. Thus, a completely HLA-mismatched standard criteria donor

kidney has a better probability of long-term survival than an HLA-matched kidney from an expanded criteria donor. Expanded criteria donor kidneys are still offered to HLA-matched candidates, but the time for accepting these offers has been reduced, and few are accepted.

Antigens are considered as “matches” using definitions that take into account the capability of HLA laboratories to distinguish one antigen from another. For example, a donor's HLA-B14 antigen would match a recipient typed as B14, B64, or B65 (splits of B14). A donor with HLA-DR16 would match a recipient with DR2, DR15, or DR16. These equivalences are based on laboratories reaching greater than 90% consensus in their ability to type the “split” antigens. So far, there is no evidence that marked improvements in graft survival could be achieved by matching kidneys at the allele level. In fact, many recipients with HLA-mismatched kidney grafts continue to have good function many years after transplantation, suggesting that some HLA mismatches may be more deleterious than others. If those combinations could be identified, it would reduce the number of HLA specificities that should be matched for organ sharing.

Among recipients of living donor transplants, however, the effect of HLA matching on long-term graft survival differs from the effect on deceased donor transplants as shown in Figure 3.3. Although transplantations between HLA-identical siblings provide the best long-term success rates (77% of these grafts still survive at 10 years), the number of HLA antigen mismatches has little effect on the survival of mismatched grafts. Surprisingly, kidneys from genetically unrelated donors have had nearly the same long-term graft survival rates as grafts between one-haplotype-matched siblings or parents and their offspring (about 64% at 10 years). This observation has fueled a rapid increase in the number of unconventional living donor transplants during the past decade.

The results of living donor transplants are superior to those of deceased donor transplants, even for recipients of HLA-matched kidneys.

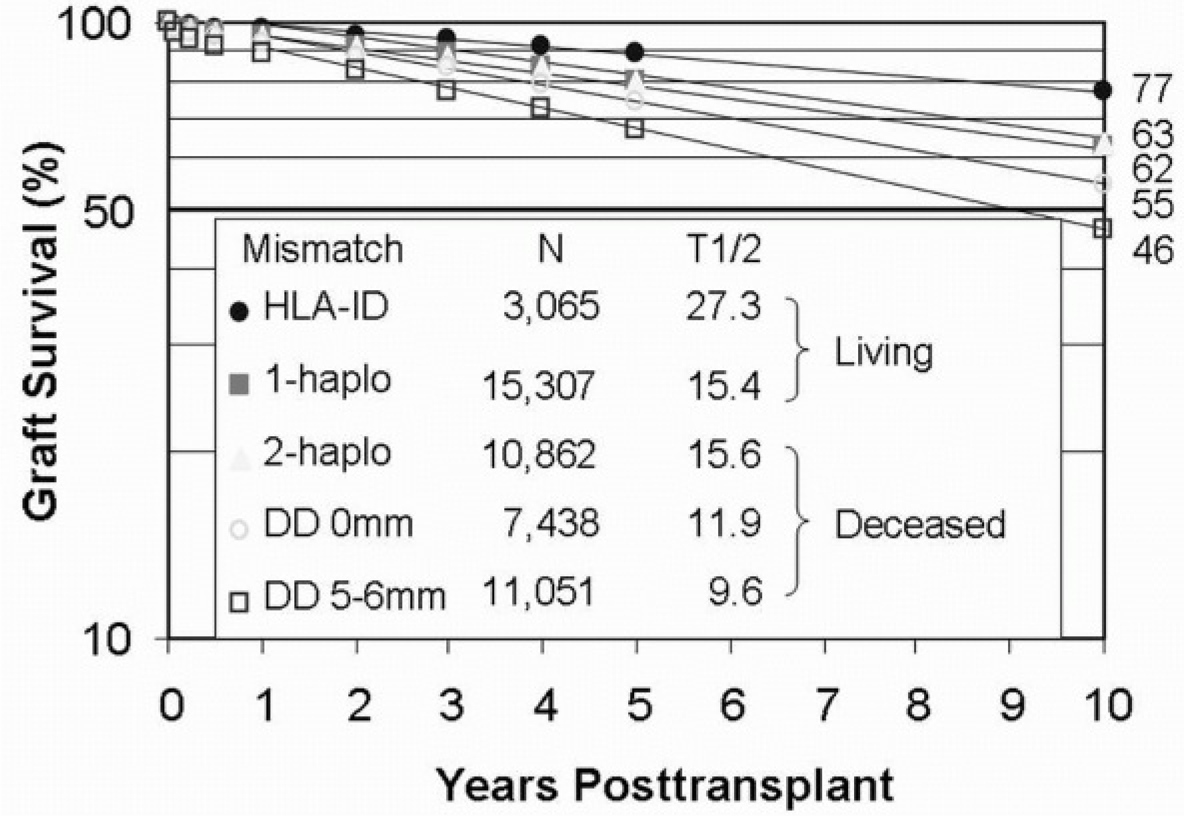


FIGURE 3.3 Projected 10-year graft survival rates for recipients of living donor kidney transplants according to the HLA-haplotype match compared with recipients of matched and completely mismatched deceased donor kidneys. HLA-identical sibling kidneys had the highest 10-year graft survival rate (77%) and half-life (28 years), followed by living donor kidneys mismatched for one or two HLA haplotypes. Even poorly matched kidneys from living donors had better 10-year graft survival rates than HLA-matched or HLA-mismatched deceased-donor kidneys. The graft half-life is the number of years before half the grafts that survive at 1 year will fail, or the patient will die with a functioning graft. The half-life was used to estimate 10-year graft survival rates. (Data are from the OPTN/UNOS Registry and were collected between 1998 and 2003 with follow-up to May 2008).

IMMUNE MONITORING

Current methods used to diagnose renal allograft rejection depend on changes in blood chemistry markers, such as creatinine levels or blood urea nitrogen (BUN). However, these markers are, at best, surrogate markers for rejection, and clearly rejection must precede the deterioration in graft function. Although diagnosis of rejection by histopathologic examination of renal biopsies remains the gold standard (see Chapter 14), there is a need for a less-invasive approach for the early detection of immunologic events leading to rejection. A promising area in the study of renal allograft rejection is the identification of biomarkers of immune alloreactivity to the graft. Monitoring the immune response to the allograft permits the early identification of patients at risk for

rejection and graft loss, optimization of drug regimens, monitoring responses to therapy after intervention, and guide the development of new immunosuppressive therapies. Immune monitoring might aid in differentiating rejection from other forms of graft dysfunction such as primary nonfunction and drug toxicity. The potential of this approach to reduce the cost associated with graft rejection while maximizing patient and graft survival is tremendous. The following sections outline some of the common and newly developed cellular, humoral, genomic, and proteomic assays to assess the immune status of the transplant recipient.

Monitoring Anti-Human Leukocyte Antigen Antibodies After Transplantation

Acute humoral rejection occurs during the early post-transplantation period and can lead to rapid deterioration of graft function (see Chapter 9). The primary histopathologic feature is the deposition of complement in the graft as measured by C4d immunostaining (see Chapter 14). Humoral rejection may also play a role in chronic rejection. Studies show that patients developing anti-HLA antibodies after transplantation are at high risk for both acute and chronic rejection and graft loss. The development of donor-specific anti-HLA antibodies to class I or class II antigens after renal transplantation strongly correlates with C4d deposition in the graft and appears to be a specific marker of antibody-dependent vascular injury. Anti-HLA antibody production may also predict chronic allograft rejection. Immune monitoring of anti-HLA antibodies can be used to guide immunotherapy and permit early intervention.

The methods and approaches for the detection of anti-HLA antibodies are identical to those used in pretransplantation evaluation. Detection of anti-HLA antibodies by complement-dependent lymphocytotoxicity has the benefit of identifying antibodies that fix complement and are clearly detrimental to the graft. However, the more recently developed solid-phase flow cytometry and ELISA tests using purified HLA antigen are more useful for post-transplantation monitoring because they are more sensitive and can identify the isotype and specificity of the anti-HLA antibody. Alternatively, the production of anti-HLA antibodies can be monitored by directly crossmatching recipient sera with donor lymphocytes using complement-dependent lymphocytotoxicity and flow cytometry methods.

Cellular Tests

The mechanisms underlying allograft rejection are not completely understood, although it has become increasingly clear that recipient T cells become activated on direct recognition of HLA/peptide complexes present on the membrane of passenger dendritic cells of donor origin. This vigorous response, which appears to violate the rule of self-MHC restriction, is driven primarily by

antigenic mimicry. T cells activated through the direct recognition pathway are

thought to be important for initiation of early acute rejection. However, these directly activated T cells appear to play a less important role after the departure of donor dendritic cells from the graft because on recognition of donor HLA molecules on “nonprofessional” antigen-presenting cells (APCs) that lack costimulatory elements, they may become anergized. Several recent studies indicate that the indirect recognition pathway, which is stimulated by allopeptides presented by professional APCs of host origin, is a major contributor to rejection, especially chronic rejection. Helper T cells engaged in the direct and indirect pathway provide lymphokines required for the proliferation and maturation of cytotoxic T cells and of anti-HLA antibody-producing B cells. The helper T cells may also produce cytokines, invoking a delayed-type hypersensitivity response. The direct recognition pathway is thought to be the primary mediator of acute allograft rejection and can be measured *in vitro* by the strength of the antidonor mixed lymphocyte culture (MLC) assay and cell-mediated lympholysis (CML) reactivity exhibited by recipient T cells.

Cell-Mediated Lympholysis and Mixed Lymphocyte Culture Assays

The CML assay measures the cytotoxic T-cell reactivity to mismatched HLA class I antigens of the donor. The MLC assay measures the capacity of recipient leukocytes to respond to HLA class II differences expressed by donor leukocytes. The degree of T-cell proliferation when leukocytes from the recipient are cocultured with irradiated leukocytes from the donor represents a functional measure of the degree of histocompatibility differences between individuals. T-cell proliferation or cell division is measured by incorporation of radioactive thymidine into proliferating cells. Alternatively, cell division can be followed using a novel flow cytometric assay that uses the intracellular fluorescent label carboxyfluorescein diacetate succinimidyl ester (CSFE) to tag proliferating cells. The intensity of the CSFE tag is reduced at each cell division, thereby permitting the extrapolation of the number of cells responding to an antigen. Another approach for determining cell activation and proliferation involves the measurement of the nucleotide adenosine triphosphate (ATP). The cell produces ATP during activation with a mitogen or specific antigen, and the quantity is directly related to the strength of the immune response. ATP is measured by addition of firefly luciferase and luciferin in the presence of magnesium ions.

Traditionally, the CML and MLC tests were used in the pretransplantation evaluation of donor-recipient pairs. More recently, these tests have been used in the post-transplantation setting to identify patients who are hyporesponsive and who display decreased alloresponses to the donor. Donor antigen-specific hyporesponsiveness, defined as a significantly lower MLC or CML between the recipient and donor after transplantation, has been observed in recipients of kidney, heart, lung, and liver transplants. Several studies report that the hyporesponsive state is associated with a lower incidence of chronic rejection and improved graft outcome. However, not all investigations confirm this finding, and variation may be explained by differences in the

techniques used and interpretation of test results. For instance, the CML assay primarily measures class I alloreactivity through the direct pathway, whereas the MLC test recognizes class II differences between the recipient and donor by both the direct and indirect recognition pathways.

Precursor Frequency Analysis

The indirect recognition allorecognition pathway is thought to play an important role in mediating chronic allograft rejection. Patients who are at risk for chronic rejection of heart, renal, lung, and liver allografts can be identified by

an increased capacity for indirect recognition of donor HLA allopeptides. Persistent allopeptide reactivity and epitope spreading are both characteristic of chronic allograft rejection. The precursor frequency of alloreactive T cells recognizing mismatched donor HLA antigens, measured by limiting dilution analysis, provides a means of assessing the indirect pathway. T-cell precursor frequency can also be measured by an enzyme-linked immunosorbent spot assay (ELISPOT), which has the advantage of detecting cytokine-secreting antigen-specific cells. In the ELISPOT assay, tissue culture plates are coated with antibodies specific for the cytokine of interest, and cells, together with antigen, are added to the plates. Cytokines produced by the antigen-specific cells are detected using a secondary reporter antibody. Cytokine-secreting cells are enumerated using an automated computer-assisted image analyzer. Alternatively, cytokine-secreting antigen-specific T cells can be detected using flow cytometry. After activation, the secreted cytokines are captured onto the surface of the cell and enumerated using an anticytokine antibody conjugated with a fluorescent dye. Both the ELISPOT and flow assays are up to 400-fold more sensitive than the detection of cytokines in supernatants and can detect antigen-specific cells at the single-cell level.

Tetramers

Antigen-specific T cells can also be detected using HLA class I and class II tetramers. The HLA tetramer is created by generating recombinant HLA class I or class II molecules that are folded together with antigenic peptides to form monomers conjugated with biotin. The monomers are assembled into tetramers by adding avidin conjugated with a fluorochrome. Antigen-specific T cells can be detected at a frequency of 10^{-4} to 10^{-5}, and tetramers have been used to monitor immunity to infectious agents, vaccines, autoantigens, and tumors by flow cytometry. Their potential use in monitoring alloimmune responses is currently unknown and may be hindered by the numerous peptides typically presented by MHC molecules.

Cellular assays have been used to detect alloantigen-specific T cells both in the peripheral blood and in the allograft. Characterization of graft-infiltrating cells identifies populations of cells that are likely participating in pathologic processes such as transplant rejection. The ability to detect interleukin (IL-2)-positive T cells in graft

infiltrates correlates with both acute and chronic rejection. The disadvantage of this approach is that it involves obtaining a biopsy sample, which is an invasive procedure and clearly not suitable for routine monitoring.

In addition to identifying patients at risk for rejection, the cellular assays described previously may be useful for monitoring the effectiveness of immunosuppressive agents and for identifying patients who can successfully undergo withdrawal of immunosuppressive drugs. Currently, immunosuppressive drugs are administered based on body weight, and drug dose is monitored using biochemical assays. Unfortunately, these biochemical assays do not provide an indication of the effectiveness of the drug regimen on immune function. Because the major immunosuppressive agents used inhibit calcineurin, a key enzyme involved in T-cell activation, assays quantitating mitogen or antigen-specific T-cell activation in the peripheral blood of transplant recipients have the potential to evaluate the effectiveness of an immunosuppressive regimen. Monitoring studies also permit real-time analysis of the immune response to changes in therapy, ultimately offering individualized therapy.

Gene Expression Assays

Technologic advances in the field of molecular genetics allow measurement of the expression of immune activation and effector molecules involved in transplant rejection. Rapid measurement of gene expression by real-time PCR provides an accurate assessment of RNA levels in recipient blood or the donor allograft that can be used to diagnose rejection in the clinical setting. The main limitation of monitoring expression of immune activation genes for diagnosis of rejection is that these same markers can also be elevated during viral and bacterial infections.

Microarrays have also been used to provide global insights into the mechanisms of allograft dysfunction and rejection as well as tolerance. Although the cost of this technology precludes it from being used as a routine monitoring tool at this time, genome-wide analysis by microarrays has the potential to identify novel surrogate markers of graft rejection that can be validated in a larger number of clinical samples using real-time PCR. Analysis of differentially expressed genes in the peripheral blood of solid organ allograft recipients diagnosed with acute rejection has led to the identification of genes and proteins predominantly involved in cell migration (chemokines), cellular activation (costimulatory and adhesion molecules and cytokines), and cellular cytotoxicity (granzyme B and perforin) and are discussed briefly next.

Cellular Cytotoxicity

One group of rejection markers includes proteins released by T lymphocytes during the rejection process. Two such proteins are perforin and granzyme. Perforin is a protein in the cytoplasmic granules of T lymphocytes that, on release, can disrupt the lipid

membranes of foreign target cells and derange endosomal trafficking within these target cells. Granzyme appears to depend on perforin for its effective delivery to the foreign target cell. Once granzyme has accessed the target cell, it can trigger cell death through apoptosis. As T lymphocytes infiltrate the transplant at the time of rejection, they release perforin and granzyme; high levels of these proteins have been found in tissue, peripheral blood, bronchoalveolar lavage, and urine specimens in rejecting lung, heart, liver, kidney, small bowel, and pancreas allografts, making perforin and granzyme excellent markers of rejection.

Chemokines and Chemokine Receptors

The migration of leukocytes from the peripheral circulation to the allograft is regulated by complement components, platelet-activating factors, and chemotactic cytokines, called *chemokines*. The chemokines CXCR3, CXCR4, CX3CR1, and CCR5 and their ligands interferon-γ inducible protein 10 (IP-10), RANTES, MIP-1α, and MIP-1β were frequently identified during rejection in microarray studies, and their importance in transplant rejection has been documented in numerous studies.

Cellular Activation

The activation of naive T cells is governed by an antigen-specific signal (signal 1) through the T-cell receptor recognizing an MHC-peptide complex, and an antigen nonspecific accessory signal (signal 2) provided by costimulatory molecules of the B7 family (CD28, ICOS) and tumor necrosis factor receptor (TNFR) family (CD154, CD134, CD27). Negative costimulatory signals mediated through cell surface molecules such as CTLA-4 (cytotoxin T-lymphocyteassociated protein-4, or CD152) and PD-1 play a critical role in down-modulating immune responses and maintaining peripheral tolerance.

FOXP3 is a transcription factor that regulates the differentiation of $CD4^+$, $CD25^+$ regulatory T cells. Strong expression of FOXP3, together with perforin and granzyme B, identified renal allograft recipients with resolving rejection.

Cytokines

IL-2 is an important growth factor for T-cell activation. IL-2 mediates its biologic effects through binding to the IL-2 receptor. The IL-2 receptor is not expressed on normal or unstimulated lymphocytes, but it is rapidly transcribed and expressed on activated T cells. Increased expression of IL-2 receptor has been detected in heart, lung, and renal biopsies with acute rejection by real-time PCR and by microarray. Elevation in soluble IL-2 receptor levels correlates with renal and liver allograft rejection. T-cell growth factor-β is a fibrogenic cytokine whose expression is strongly associated with chronic rejection in animal models and humans.

Biomarkers of Tolerance

Long-term allograft survival typically requires lifelong immunosuppression. On rare occasions, transplant recipients develop “operational tolerance” with stable graft function in the absence of immune suppression. Recent studies indicate that identification of operational tolerance in renal transplant recipients is possible by assessing gene expression pattern recognition across a modest number of genes in the peripheral blood. The gene signature suggests a pattern of reduced costimulatory signaling, immune quiescence, apoptosis, and memory T-cell responses. Monitoring for peripheral tolerance using blood samples may have utility to guide immunosuppression minimization therapy.

Proteomic Assays

Proteomics is defined as the study of the proteome, which includes all proteins encoded by genes of an organism. Proteomic assessment of biomarkers of transplant rejection and tolerance have typically been based on immunologic methods such as Western blot analysis, ELISA, and Luminex assay. Several studies have demonstrated the utility of measuring soluble and secreted proteins to identify patients at risk for transplant rejection. For example, monitoring soluble CD30 levels in recipients of renal allografts has been reported to be an independent and highly predictive factor of immunologic risk. New discovery approaches have been developed using mass spectrometry that permit an unbiased approach to simultaneously analyze numerous proteins and peptides associated with a pathologic processes. The most widely used technology is two-dimensional gel electrophoresis, which provides excellent resolution of proteins from 10 to 150 kDA. Another technology is SELDI-TOF mass spectrometry, which combines surface chromatography with matrix-assisted laser desorption ionization time-of-flight mass spectrometry to identify proteins in complex mixture. Recent studies employing this technology detected increased urinary proteins, such as β_2-microglobulin and α_1-antichymotrypsin, in patients with acute renal allograft rejection.

The immune response to the transplant is dynamic, and it is unlikely that one single assay will accurately assess the immune status of the patient. We suggest that a panel of assays will be used to monitor different components of the immune response (humoral versus cellular) to provide an accurate profile of the patient. Monitoring of gene expression and proteomic profiles should enhance our understanding of transplant pathophysiology and help to identify novel biomarkers of rejection, tolerance, and targeted therapies.

Selected Readings

Bartel G, Wahrmann M, Exner M, et al. In vitro detection of C4d-fixing HLA alloantibodies: associations with capillary C4d deposition in kidney allografts. Am J

Transplant 2008;8:41-49.

Bielmann D, Hönger G, Lutz D, et al. Pretransplant risk assessment in renal allograft recipients using virtual crossmatching. Am J Transplant 2007;7:626-632.

Bjorkman PJ, Saper MA, Samraoui B, et al. Structure of the human class I histocompatibility antigen, HLA-A2. Nature 1987;329:506-512.

Bray RA, Nolen JD, Larsen C, et al. Transplanting the highly sensitized patient: The Emory algorithm. Am J Transplant 2006;6:2307-2315.

Cai J, Terasaki PI, Mao Q, et al. Development of nondonor-specific HLA-DR antibodies in allograft recipients is associated with shared epitopes with mismatched donor DR antigens. Am J Transplant 2006;6:2947-2954.

Chua MS, Sarwal M. Microarrays: new tools for transplantation research. Pediatr Nephrol 2003;18:319-327.

Gebel HM, Bray RA, Nickerson P. Pre-transplant assessment of donor-reactive, HLAspecific antibodies in renal transplantation: contraindication vs. risk. Am J Transplant 2003;3:1488-1500.

Gloor JM, DeGoey SR, Pineda AA, et al. Overcoming a positive crossmatch in living-donor kidney transplantation. Am J Transplant 2003;3:1017-1023.

Gloor JM, Sethi S, Stegall MD, et al. Transplant glomerulopathy: subclinical incidence and association with alloantibody. Am J Transplant 2007;7:2124-2132.

Hernandez-Fuentes MP, Warrens AN, Lechler RI. Immunologic monitoring. Immunol Rev 2003;196:247-264.

Jordan S, Cunningham-Rundles C, McEwan R. Utility of intravenous immune globulin in kidney transplantation: efficacy, safety, and cost implications. Am J Transplant 2003;3:653-664.

Jordan SC, Vo AA, Peng A, Toyoda M, Tyan D. Intravenous gammaglobulin (IVIG): a novel approach to improve transplant rates and outcomes in highly HLA-sensitized patients. Am J Transplant 2006;6:459-466.

Le Bas-Bernardet S, Hourmant M, Valentin N, et al. Identification of the antibodies involved in B-cell crossmatch positivity in renal transplantation. Transplantation 2003;75:477-482.

Li B, Hartono C, Ding R, et al. Noninvasive diagnosis of renal-allograft rejection by measurement of messenger RNA for perforin and granzyme B in urine. N Engl J Med 2001;344:947-954.

Marsh SG, Albert ED, Bodmer WF, et al. Nomenclature for Factors of the HLA System, 2004. Hum Immunol 2005;66:571-636.

Mizutani K, Terasaki P, Bignon JD, et al. Association of kidney transplant failure and antibodies against MICA. Hum Immunol 2006;67:683-691.

Mizutani K, Terasaki P, Hamdani E, et al. The importance of anti-HLA-specific antibody strength in monitoring kidney transplant patients. Am J Transplant 2007;7:1027-1031.

Patel R, Terasaki PI. Significance of the positive crossmatch test in kidney transplantation. N Engl J Med 1969;280:735-739.

Pei R, Lee JH, Shih NJ, et al. Single human leukocyte antigen flow cytometry beads for accurate identification of human leukocyte antigen antibody specificities. Transplantation 2003;75:43-49.

Reinsmoen NL. Cellular methods used to evaluate the immune response in transplantation. Tissue Antigens 2002;59:241-250.

Sarwal MM. Chipping into the human genome: novel insights for transplantation Immunol Rev 2006;210:138-155.

Schreuder GM, Hurley CK, Marsh SG, et al. HLA dictionary 2004: summary of HLA-A, -B, -C, -DRB1/3/4/5, -DQB1 alleles and their association with serologically defined HLA-A, -B, -C, -DR, and -DQ antigens. Hum Immunol 2005;66:170-210.

The MHC Sequencing Consortium. Complete sequence and gene map of a human major histocompatibility complex. Nature 1999;401:921-923.

Vo A, Lukovsky M, Toyoda M, et al. Rituxmab abd intravenous immune globulin for desensitization during renal transplantation. N Engl J Med 2008;359:242-251.

Zachary AA, Montgomery RA, Ratner LE, et al. Specific and durable elimination of antibody to donor HLA antigens in renal-transplant patients. Transplantation 2003;76:1519-1525.

4

The Science of Deceased Donor Kidney Transplantation

Kevin J. O'Connor

Francis L. Delmonico

H. Albin Gritsch

Gabriel M. Danovitch

Kidney transplantation cannot proceed without kidney donors, and although much emphasis is justifiably given to post-transplantation patient management, the appropriate identification and preparation of both living and deceased donors contribute critically to the success of the transplantation endeavor on the individual, national, and international levels. As of 2009, living donors and deceased donors each account for about half of all kidney transplantations performed in the United States. Although most transplantation centers regard living donation as the preferred donation modality for individual patients with advanced kidney disease, the therapeutic potential of deceased organ donation must be maximized not only for kidneys but also for other solid organs for which living donation is not an option (or a limited option in the case of liver transplantation). Efforts to enhance deceased donor transplantation are essential to minimize the burden on living donors and on recipients who do not have the option of living donation (see Appendix, Declaration of Istanbul).

There are wide variations in the use of living and deceased kidney donors around the world (see Chapter 1, Fig. 1.3). These differences reflect varying medical and societal cultural values and varying realities in the availability of sophisticated care for patients with advanced kidney disease (see Chapter 1, Fig. 1.2). Differences can also be driven by the availability of deceased donor organs relative to the number of patients waiting for transplants, attitudes of local physicians regarding the risks of living donation, national deceased donor legislation, and the degree of government oversight. In Spain, for example, where a highly effective mechanism for identifying deceased donors has helped keep waiting lists short, living donation accounts for less than 5% of all transplantations. In Japan, however, strong cultural and, until recently, legal barriers have limited deceased donor transplants, resulting in living donation as the most common form of transplantation.

In the United States, the supply of deceased organ donors and kidneys has increased. There were close to 11,000 deceased donor kidneys transplanted in 2009, an increase of 25% over the previous 5 years. Much of this increase has been attributed to the effectiveness of the Organ Donation and Transplantation Breakthrough Collaborative sponsored by the Health Resources and Services Administration (HRSA). Despite this large increase in the supply of deceased donor kidneys in this “Collaborative era,” the total number of renal transplant candidates on the waiting list continues to increase each year and reached about 80,000 as of early 2009. The rate of expansion of the list reflects the number of new registrants minus the number of patients who receive transplants from living and deceased donors and the number of patients who die while awaiting a transplant or who are removed from the list for other reasons. About one third of those registered, however, are listed as “inactive” and therefore deemed ineligible for transplantation at a given point in time (see Chapter 7, Part II). Currently, the number of transplants performed each year approximates the number of new “active” candidates on the list.

TABLE 4.1 Deceased Donor Process: From Donor Identification to Transplantation

Donor identification
Imminent death—eligible death
Referral to organ procurement organization
Assessment of donor suitability
Consent for donation

Organ donor intensive care unit management
Organ allocation
Organ recovery surgery
Organ preservation and transportation
Organ transplantation

This chapter addresses the various aspects of deceased donor kidney transplantation. The term *science* of deceased organ donation was adopted to capture the nuanced complexity of its medical, ethical, organizational, and societal aspects and to reflect on the fact that we have much to learn about how to optimize the procedure. The chapter is divided into three parts. The first part addresses the selection and preparation of deceased donors; the second part addresses the surgical technique of deceased organ donation and organ preservation; and the third part addresses the allocation of deceased donor kidneys to the kidney transplant waiting list.

PART I. DIAGNOSIS OF DEATH AND IDENTIFICATION, SELECTION, AND PREPARATION OF DECEASED DONORS

The deceased donor organ donation process can be viewed as a continuum from the first identification of the potential organ donor through to the transplantation of renal (and other) allografts at the transplantation center (Table 4.1). To maximize the supply and quality of the deceased donor kidney pool, every step in this continuum needs to be optimized, as described next.

Diagnosis of Death

Traditionally, in the lay, legal, and medical communities, death has been determined by an irreversible cessation of cardiac and respiratory function. The concept of brain death emerged in the 1960s as a response to the ability to resuscitate individuals and

mechanically maintain cardiac and respiratory function. The terms *brain death* and *cardiac death* are employed in this chapter because of their widespread use and familiarity. These terms are not ideal and may be a source of confusion and distress in the lay community and among donor families because of understandable but unsubstantiated concern that brain-dead donors are not truly dead. The terms *death determined by neurologic criteria* and *death determined by cardiorespiratory criteria* are preferable.

Diagnosis of Brain Death

Most organ donors have severe brain injury and present to the hospital with a low Glasgow Coma Scale score (Table 4.2). Most deceased organ donors are brain dead. Proper diagnosis of brain death is essential to the organ donation process

and to maintaining public trust and acceptance of organ donation from brain-dead organ donors. Among the lay public, there is often a troubling confusion between the diagnosis of brain death and that of a persistent vegetative state. The criteria for diagnosis and declaration of brain death are well described (Table 4.3) and require irrefutable documentation. They include a known cause of brain injury, irreversibility, and absence of cerebral and brainstem function, including apnea. *The diagnosis of brain death should be made by a physician who is independent of the transplantation team* and thus free of conflict of interest. Ancillary testing is not mandated but may include electroencephalography, conventional angiography, radionuclide angiography, magnetic resonance angiography, computed tomographic angiography, transcranial Doppler, and somatosensory evoked potentials. Indications for pursuit of ancillary testing include toxic drug levels, inconclusive apnea testing, normal neuroimaging, inability to complete a clinical examination, and chronic CO_2 retention.

TABLE 4.2 Glasgow Coma Scale

Response	**Score***
Eyes Open	
Spontaneous	4

To speech	3
To pain	2
Absent	1
Verbal	
Converses, is oriented	5
Converses, is disoriented	4
Inappropriate	3
Incomprehensible	2
Absent	1
Motor	

Obeys	6
Localizes pain	5
Withdraws (flexion)	4
Decorticate (flexion) rigidity	3
Decorticate (extension) rigidity	2
Absent	1

* The sum obtained in this scale is used to assess coma and impaired consciousness: mild is 13 to 15 points; moderate is 9 to 12 points; severe is 3 to 8 points. Patients with a score of less than 8 are in a coma.

(From Teasdale G, Jennet B. Assessment of coma and impaired consciousness: a practical scale. Lancet 1974;304:81-84, with permission.)

Diagnosis of Cardiac Death

The term *donation after cardiac death* (DCD) is preferred to the term *non-heart-beating donor* (NHBD) because of the parallel to the more common *donation after brain death*. Before the acceptance of criteria for the declaration of brain death, all deceased donor organs were recovered from patients with cardiac arrest. With the broad acceptance of brain death criteria and the development of multiorgan recovery, the use of DCD

organs decreased substantially because

of the risks associated with ischemic damage. The organ donor shortage has led to a reevaluation of this policy.

TABLE 4.3 Clinical Criteria for Diagnosis of Brain Death

Irreversibility
No sedating, paralyzing, or toxic drugs
No gross electrolyte or endocrine disturbances
No profound hypothermia
Absent Cerebral Function
No seizures or posturing
No response to pain in cranial nerve distribution*
Absent brainstem function

Apnea in response to acidosis or hypercarbia
No pupillary or corneal reflexes
No oculocephalic or vestibular reflexes
No tracheobronchial reflex

* Spinal reflexes may be present.

There has been a steady increase in the fraction of DCD donors in the United States (see Fig. 4.1). There are four so-called Maastricht categories of DCD donors (Table 4.4). Category I and II DCD donors, also referred to as *uncontrolled donors,* are pulseless and asystolic after adequate but failed attempts at resuscitation. Some trauma centers have developed protocols to minimize ischemia in these circumstances by rapid placement of intravenous cannulas to cool the organs after death has been declared. The option to donate is preserved until the family can be informed of the death and then counseled by the organ procurement staff. If consent to donate is obtained, the organs are recovered quickly to prevent further ischemic injury.

Uncontrolled DCD is the most common form of DCD in Spain and Japan. In the United States, DCD is usually category III or "controlled." These donors are comatose, irreversibly brain damaged, and respirator dependent, but are not brain dead by strict definition. In these circumstances, the decision to withdraw supportive care is made by the family and primary medical team, and appropriate consent for organ donation is obtained after the decision to withdraw support. Ventilator support is discontinued either in the operating room or in an intensive care unit, cardiac function is monitored, and death is pronounced by standard cardiac criteria after a predetermined (usually 5-minute) period of asystole. Organ recovery then proceeds expeditiously. *The organ recovery team plays no part in the diagnosis of death or medical management of the patient before asystole*. Maastricht category IV DCD donors are also known as "crashing donors," who have often become hemodynamically unstable en route to organ recovery after a diagnosis of brain death.

It has been estimated that if DCD protocols were maximized, the supply of deceased donor organs could increase considerably. DCD is associated with an increased rate of delayed graft function, but long-term graft survival is similar to that of brain-dead donors. It is critical that protocols for DCD be ethically sound, respect the feelings of donor families and medical staff, and avoid any appearance of conflict of interest. As of 2007, all organ procurement organizations (OPOs) and transplant centers in the United States must develop and comply

with protocols to facilitate recovery of organs by DCD. The model elements of DCD protocols are summarized by Steinbrook (see "Selected Readings").

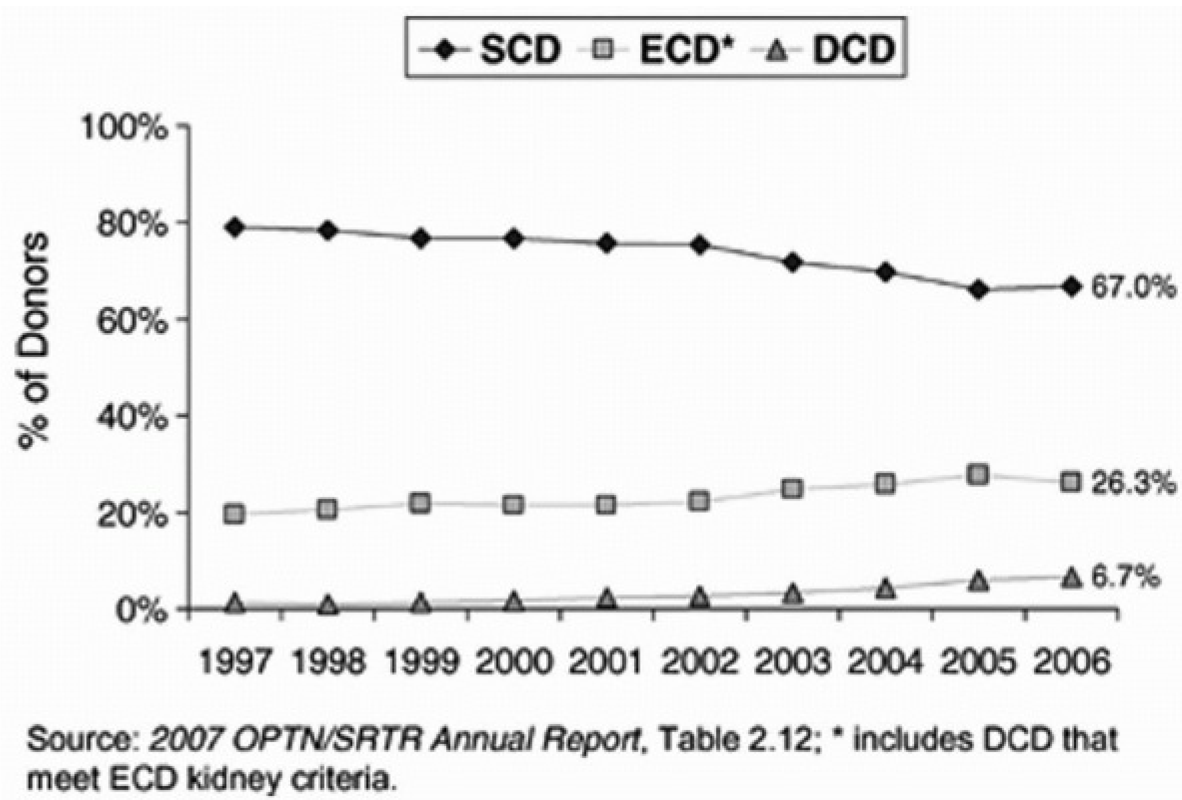


FIGURE 4.1 Deceased donor population by donor type and year in the United States. (From Sung RS, Galloway J, Tuttle-Newhall J, et al. Organ donation and utilization in the United States 1997-2006. Am J Transplant 2008;8(Pt 2):922-934, with permission.)

Donor Identification and Referral

Prompt identification of all potential organ donors is critical to efforts to maximize organ donation and transplantation. Potential organ donors may be identified in the emergency department or in the critical care unit. Most deceased organ donors have suffered severe nonsurvivable brain injury, traumatic or otherwise, and are first seen in the emergency department, then transferred to the intensive care unit. A small subset

of potential DCD donors present with terminal respiratory failure or end-stage neurodegenerative disease such as amyotrophic lateral sclerosis. Vigilant surveillance for potential organ donors on the part of emergency and critical care staff is paramount to ensure that every opportunity is realized. In the United States, hospitals are required by the Center for Medicare and Medicaid Services (CMS) to identify and refer all potential organ donors to the local OPO. The term *imminent death* has been used to define those patients who should be referred to the OPO as one of several performance metrics routinely monitored by CMS (Table 4.5).

TABLE 4.4 Maastricht Categories for Non-Heart-Beating Donors

Category I: dead on arrival
Category II: unsuccessful resuscitation
Category III: awaiting cardiac death
Category IV: cardiac death in a brain-dead donor

TABLE 4.5 Definition of Imminent Death

A patient with severe, acute brain injury, who:

1. Requires mechanical ventilation, and

2. Is in an intensive care unit or emergency department, and

3. Has clinical findings consistent with a Glasgow Coma

Scale score that is less than or equal to a mutually agreed on threshold (e.g., 4 or 5); or

- For whom physicians are evaluating a diagnosis of brain death; or

- For whom a physician has ordered that life-sustaining therapies be withdrawn, pursuant to the family's decision.

(Adapted from Shafer TJ, Wagner D, Chessare J, et al. Organ Donation Breakthrough Collaborative: increasing organ donation through system redesign. Crit Care Nurse 2006;26:33-48.)

Imminent death refers to patients who are likely to die in the hospital in a manner that would enable consideration of organ donation following their death. To this end, hospitals collaborate with OPOs to operationalize the identification of imminent deaths, usually by developing explicit, objective clinical criteria for contacting the OPO. One commonly employed approach is to consider any ventilator-dependent patient with a Glasgow Coma Scale score of 5 or less who is expected to die in the hospital as a potential organ donor to be referred to the OPO. This includes patients who are being evaluated for brain death as well as patients whose families and care team have elected to withdraw support and allow cardiac death in the face of a devastating nonsurvivable brain injury. The impact of evolving end-of-life decision-making practices and elective withdrawal of life support on the underlying potential pool of organ donors is unclear and warrants further study. Standardized definitions for key elements of the organ donation process are described in Table 4.6.

The Spanish Model

High organ donation rates reported in Spain are attributed to the so-called Spanish model of organ donation, which entails a systematic approach to maximizing the identification, referral, consent rate, and management of potential deceased organ donors. Key elements of this model include compensated and well-trained staff physicians with clearly defined accountability for effectiveness in donor surveillance and referral and aggressive pursuit of older donors. Importantly, Spain operates within a presumed consent legal framework that assumes all suitable patients, upon death, will donate their organs (see Chapter 18). Living individuals are free to opt out of these arrangements in advance if they so wish, and families retain the right to refuse permission for their family member's organs to be donated at the time of their death. The Spanish-based Organizacion Nacional de Transplantes (http:/www.ont.es) has done much to disseminate effective deceased donor management practices throughout the Spanish-speaking world.

Donation Performance

When comparing measures of donation performance between geographic areas, the metric *donors per million population* (DMP) is often used. Although this metric is convenient, its usefulness is limited. A more meaningful method for assessing and comparing organ donation rates uses the number of medically suitable potential organ donors in a geographic area as the denominator, and the number of actual organ donors in that area as the numerator. This metric is known as the *conversion rate* for organ donation and has been an effective tool for monitoring improvement in organ donation. The mean conversion rate in the United States varies regionally between 60% and 80% as of 2007, and a national target of 75% has been set.

TABLE 4.6 Organ Donor Definitions

Eligible death	Any patient aged 70 years or younger who meets the definition of death according to neurologic criteria (based on the American Academy of Neurology practice parameters for determining brain death), who does not have any of the following clinical conditions: - Tuberculosis

- HIV infection with specified conditions
- Creutzfeldt-Jacob disease
- Herpetic septicemia
- Rabies
- Reactive hepatitis B surface antigen
- Any retrovirus infection
- Active malignant neoplasms, except primary central nervous system tumors and skin cancers
- Hodgkin disease, multiple myeloma, leukemia
- Miscellaneous carcinomas
- Aplastic anemia

	- Agranulocytosis - Fungal and viral meningitis - Viral encephalitis - Gangrene of bowel - Extreme immaturity - Positive serologic or viral culture findings for HIV
Organ donor	Eligible donor from whom an organ is recovered for the purpose of transplantation after consent for donation has been obtained, including DCD (donation after cardiac death) donors and donors older than 70 years
Missed eligible referral	An imminent death in a donor who was apparently eligible but was not referred by the hospital to the organ procurement organization. Missed eligible referrals are generally discovered by an audit of a death log or by review of death record.

(Adapted from Shafer TJ, Wagner D, Chessare J, et al. Organ Donation Breakthrough Collaborative: increasing organ donation through system redesign. Crit Care Nurse 2006;26:33-48.)

The metric *organs transplanted per donor* (OTPD) is a measurement of the effectiveness of multiorgan recovery efforts. Each deceased donor is theoretically a source of two kidneys, heart and lungs, a liver, a pancreas, and intestines. The OTPD rate as of 2007 varied regionally between 2.5 and 3.25, and a national goal of 3.75 has been set by the Collaborative. Table 4.7 lists the best practices for high-performing transplantation programs from the Collaborative.

TABLE 4.7 Best Practices from High-Performing Transplantation Programs from the Transplant Growth and Management Collaborative

Driver/strategy for change	Key change concepts	Examples of action items
1. Institutional vision and commitment	Establish transplant as a high priority for health systems	Establish transplantation as a priority service for the hospital and set goals for transplant program growth
	Develop a business plan that will secure institutional investment and support	Demonstrate the clinical, economic and nonmonetary benefits of transplant
	Organize transplant services into a service line	Integrate all transplant services into a single service line with designated budget and decision-making authority

2. Dedicated team of personnel	Organize around proactive surgeons and medical doctors	Recruit and retain aggressive, experienced and high-performing surgeons and medical doctors with a passion for, commitment to and focus on growing transplantation
	Recruit, train and retain program staff who are specialized, dedicated and committed	Have transplant program staff that work exclusively on either transplant or one organ-specific transplant program
	Establish and live by a collegial, nonhierarchical team approach to care	
3. Build a financial case	Track and understand your program costs and revenues	Establish the transplant program as a separate cost center
	Negotiate payer contracts with awareness of program finances and	Model contracts and rates after program costs and actual patient resource use

	strengths	
4. Patient and family centered care	Offer a broad array of services	Offer end-stage organ care with transplant services as part of the continuum
	Educate patients and families early and often	Conduct regular, accessible education sessions for potential transplant candidates and their families about the benefits and risks of transplant and the personal and financial commitment required of patients and families
5. Practice case-based learned aggressive clinical style	Create a high threshold for refusing organs	Surgeons take all calls and there is a senior advisor always available
	Be on the cutting edge of research	Participate in innovative clinical trials, new immunotherapy regimes

(Adapted from Sung R, Galloway J, Tuttle-Newhall E, et al. Organ donation and utilization in the United States, 1997-2006. Am J Transplant 2008;8(Pt 2):925.)

Donor Evaluation

The donor evaluation process begins with an assessment of overall donor medical

suitability. Certain systemic findings, such as HIV seropositivity or active malignancy with metastases, render the donor medically unsuitable in most cases, and the donation process is terminated at this point. Absolute exclusion criteria vary among OPOs and are continuously reevaluated. Consultation with the local OPO is essential to ensure that potential organ donors are not inappropriately excluded. In light of the ongoing shortage of suitable kidneys, most other donor clinical findings are considered relative factors for the risk for transplantation-associated mortality and morbidity, and these risks must be weighed against the risk of continuing on dialysis to the patient awaiting transplantation.

Screening for potentially transmissible infectious disease in donors is discussed in Chapter 11. Serologic evaluation of organ donors includes screening for hepatitis C (HCV), HIV, human T-lymphotropic virus (HTLV), hepatitis B virus (HBV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and syphilis. Nucleic acid testing (NAT), when available, shortens the "window period" (between exposure and detection) for certain viral infections such as HIV and HCV and is especially helpful when the donor has known risk factors for HIV exposure, for example. Although HIV seropositivity is generally considered an absolute exclusion criterion, other reactive serology tests are reported to the transplantation programs at the time of the organ offer. Recipient selection may be influenced by the donor serologic profile, for example, HCV-seropositive donor kidneys may be selected for use in HCV-seropositive patients. The donor serologic findings also inform post-transplantation care of the recipient, for example, HBV prophylaxis for recipients of donor HB core antibody reactive organs (see Chapter 12). Many OPOs are now routinely performing NAT testing for HIV, HBV, and HCV, for donors at risk for infection, as an added safeguard, and to reduce the window period for detection of exposure. This may become standard practice for all organ donors in the future.

Another type of risk to be assessed is the risk for graft failure or inferior outcome. Organ quantity must be balanced with quality, factoring in the need for individual patient risk-benefit assessment (see Chapter 7). Many intrinsic donor factors have been associated with an increased risk for renal allograft failure, including donor age, donor creatinine, donor cause of death, and donor history of hypertension. The expanded criteria donor concept and the donor profile index are discussed later in the third part of this chapter (see "Allocation of Deceased Donor Kidneys in the United States").

Consent for Donation

Consent rates for organ donation have increased in the United States during the past 5 years, with a rate of more than 65% nationwide in 2007. Some regions have consent rates of close to 80%. Success in obtaining consent for organ donation is associated with highly trained, skilled, and sensitive staff, who can spend as much time as needed to support the donor family through the process. Collaboration between the health care team and the OPO staff is also essential.

Family sociodemographics (ethnicity, patient's age, and cause of death) and prior knowledge of a potential donor's wishes are significantly associated with willingness to donate. Families who reported having had conversations about organ donation were more likely to donate, as were families with more contact with OPO staff and those who experienced an optimal request.

Donor Management

Maintenance of cardiovascular stability becomes more difficult the longer the period of brain death. At the time of diagnosis, patients are often relatively

hypovolemic because of prior therapeutic attempts to minimize brain swelling by inducing dehydration. A diabetes insipidus-like state may accompany head injuries and brain death, resulting in obligatory urine outputs of up to 1 L per hour. Brain death is associated with a massive release of cytokines, a so-called cytokine storm, which has the potential to injure the donated kidney and make it more susceptible to ischemic and immunologic injury (see Chapter 9).

Blood pressure should be maintained at greater than 100 mm Hg by aggressive administration of crystalloids, colloids, or blood products. Central venous pressure should be monitored and maintained at greater than 10 mm Hg. If urine output decreases to less than about 40 mL per hour in a wellhydrated donor, furosemide or mannitol may be given. Insulin administration may be necessary to minimize hyperglycemia and glycosuria. The necessity for insulin administration does not preclude the recovery and transplantation of the pancreas (see Chapter 15). If, despite good hydration, blood pressure remains low, low-dose dopamine and other inotropic agents, such as dobutamine or norepinephrine, are sometimes required. If a hypotonic diuresis ensues, suggesting diagnosis of diabetes insipidus, a hypotonic infusion should be used to replace the urine output. Dextrose infusion, which may induce an additional osmotic diuresis, should be avoided; a vasopressin infusion may be required if the hypotonic urine volume is massive (more than 500 mL per hour). Hormonal resuscitation with methylprednisolone, triiodothyronine (T_3), and arginine vasopressin (called *3HR treatment*) may improve the quality of recovered organs.

There may be competing clinical objectives when multiple organs are being recovered. For example, lung transplant clinicians may prefer less volume replacement, as opposed to the kidney transplant clinicians who may advocate for more volume replacement to help generate a brisk diuresis. Protocols for organ donor management have been developed to adjudicate these competing interests.

PART II. SURGICAL TECHNIQUE OF DECEASED DONOR ORGAN RECOVERY

The principles of the retrieval operation are similar regardless of the organs to be

removed. Wide surgical exposure is obtained. Each organ to be removed is dissected with its vasculature intact. To avoid damage to the vasculature and to prevent delayed graft function caused by vasospasm, there is no dissection into the renal hilum. Cannulas are placed for *in situ* cooling. At the time of aortic cross-clamping, flush and surface cooling are begun. The kidneys are removed *en bloc* with the aorta and vena cava (Fig. 4.2). If multiple organs are to be removed, the preferred sequence is heart or lung first, liver or pancreas second, and kidneys last. The kidneys are protected against ischemia by the cold flush and surface cooling during the 10 to 15 minutes that it takes to remove the other organs.

One variation of this approach is a rapid infusion technique whereby cannulas are placed immediately, the aorta is cross-clamped, and the dissection is completed under cold infusion. This technique is used primarily when the donor is hemodynamically unstable.

Pharmacologic Adjuncts

Most deceased donors are given large doses of corticosteroids to deplete circulating donor lymphocytes. Mannitol, in doses of up to 1 g/kg, is also given to ensure diuresis and possibly to minimize ischemic injury. There is some evidence that α blockers, calcium channel blockers, or dopamine given intravenously before kidney manipulation may lower the rate of delayed graft function. Phentolamine (Regitine), 10 to 15 mg, may be used just before cross-clamping of the aorta; earlier use would cause significant hypotension. Systemic heparinization is carried out at the time of cannula placement with doses of 10,000 to 30,000 units.

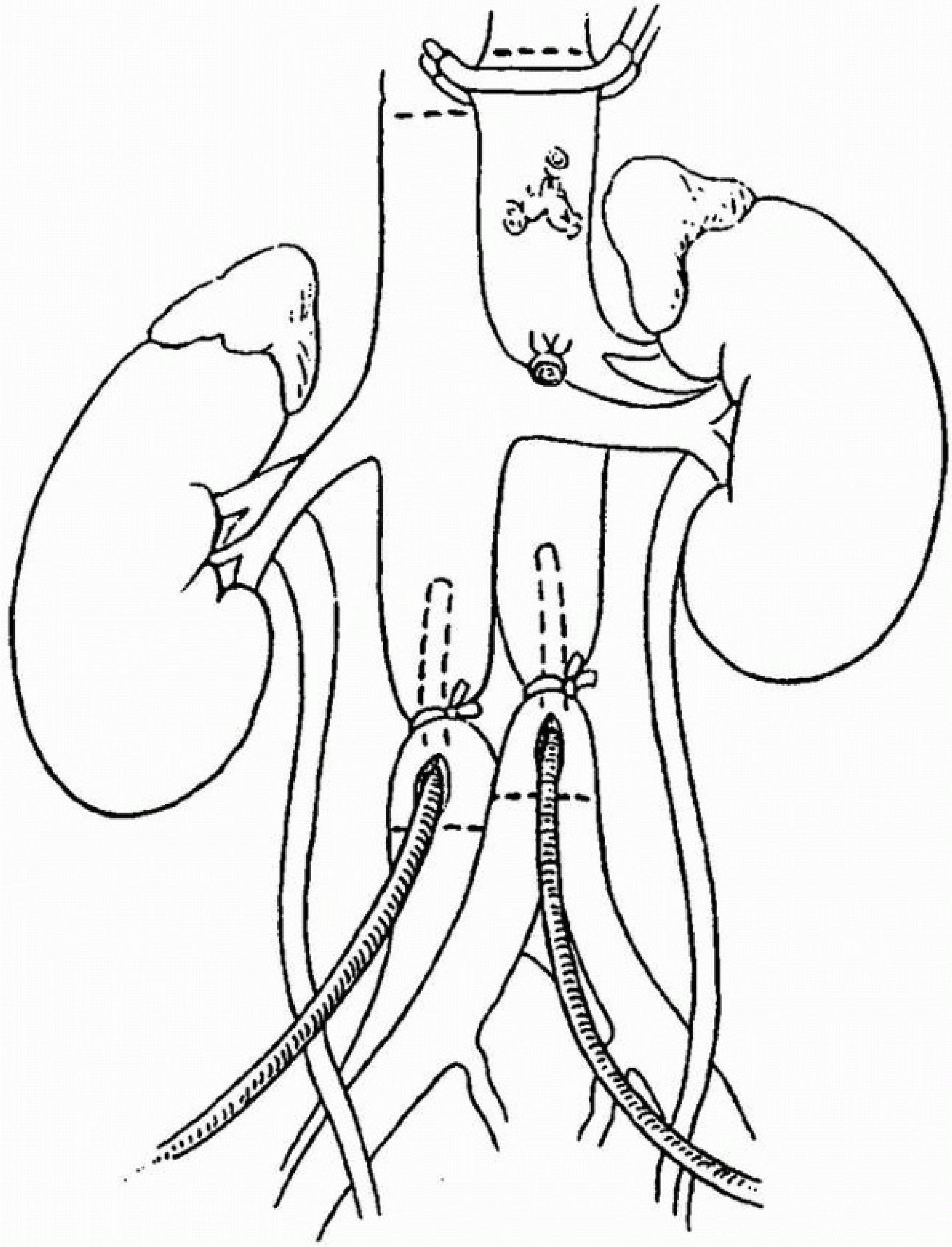


FIGURE 4.2 *En bloc* dissection for deceased donor kidney donation with cannulas in place for *in situ* perfusion. Perihilar and periureteral fat are left in place.

Ischemia Times

Warm ischemia time refers to the period between circulatory arrest and commencement of cold storage. With modern *in situ* perfusion techniques, the warm ischemia time is essentially zero in brain-dead donors, although there is warm ischemia

if hemodynamic deterioration or cardiac arrest occurs before harvest. A kidney may function after up to 60 minutes of warm ischemia, but rates of delayed function and nonfunction increase markedly after 20 minutes.

Cold ischemia time refers to the period of cold storage or machine perfusion. Short cold ischemia times are preferred. Less than 12 hours is regarded as ideal, less than 24 hours as acceptable. Most centers prefer not to use kidneys that have been in cold storage for longer than 36 hours, although an exception

may be made for kidneys whose other features are ideal. *Rewarm time* is the period from removal of the kidney from cold storage or perfusion to completion of the renal arterial anastomosis. Rewarm time can be minimized by cooling the kidney during surgery (see Chapter 8).

Organ Preservation

The two dominant methods of preserving renal allografts for transplantation are cold-storage and pulsatile preservation. Both methods employ hypothermia for maintenance of cellular viability and minimization of *ex vivo* ischemic injury. Cold-storage solutions include University of Wisconsin (UW) solution and histidine-tryptophan-ketoglutarate (HTK) solution, among others. Kidneys preserved in this fashion are flushed *in situ* through the arterial blood supply, with the preservation solution of choice, cooled to about 4° C, explanted, separated, and then packaged, bathed in the same solution in sterile containers, and stored in wet ice in coolers to maintain hypothermia until transplantation.

Hypothermic pulsatile storage delivers a dynamic flow of cold perfusate to the allograft during preservation and allows for monitoring of perfusion parameters such as flow, temperature, pressure, and renal vascular resistance. This preservation modality is commonly employed for renal allografts from older donors or those that may be compromised for other reasons (e.g., donor oliguria). Machine perfusion may allow a longer preservation time and may reduce the incidence of delayed graft function. Recovery of renal function may also be improved, and some data suggest that graft survival may be improved (see Moers and colleagues in “Selected Readings”). Serial evaluation of perfusion data help guide the decision to transplant or discard these kidneys. In general, flow rates of 100 to 150 mL/min or higher, and vascular resistance of 0.20 to 0.40, are considered optimum. Allografts with persistent low flow (less than 75 mL/min) and high resistance (>0.40) are usually declined by all centers. Long-term outcome does not appear to be influenced by the preservation techniques for ideal donors, but pulsatile perfusion may be used more often in the future.

PART III. ALLOCATION OF DECEASED DONOR KIDNEYS IN THE UNITED STATES

The establishment of the Organ Procurement and Transplantation Network (OPTN) through the National Organ Transplant Act of 1984 (NOTA, see Chapter 18) required the development of uniform national policies to describe how organs from deceased donors would be distributed to recipients. This was to ensure that patients awaiting a transplant anywhere in the United States would be transplanted in an established order. The United Network for Organ Sharing (UNOS) operates the OPTN under a contract with HRSA. The "final rule" issued in the year 2000 specifies the precise responsibilities of the OPTN. For an in-depth review of the oversight of solid organ transplantation in the United States, refer to McDiarmid and colleagues (see "Selected Readings").

Organ allocation is a major responsibility of UNOS. To operate the organ allocation system, the country is divided into organ procurement regions and areas (Fig. 4.3), with OPOs operating according to agreed on distribution and sharing criteria. A donor service area (DSA) is the geographic area serviced by the OPO with its donor hospitals and transplant programs. To be placed on the transplant waiting list, a patient must fulfill certain listing criteria (see Chapter 7). Renal transplant recipients must either be receiving chronic dialysis or, if they are not on dialysis, have a glomerular filtration rate estimated at 20 mL per minute or less. No priority is given for specific disease states, although many diabetic patients are now listed for a kidney and pancreas and may receive transplants more quickly (see Chapter 15).

FIGURE 4.3 United Network for Organ Sharing (UNOS) regions of the United States.

Point System for Deceased Donor Kidney Allocation

The order in which waiting patients are offered each kidney that becomes available is determined by a set algorithm, and waiting patients are ranked by a central computer that is located in the UNOS offices in Richmond, Virginia. Relevant information about a potential donor is made available to transplant programs on a Web-based program called *DonorNet*. The ultimate decision about whether to accept an offer for a given patient falls to the responsible physician or surgeon; however, whenever an offer is declined, a reason or refusal code must be provided to UNOS. Table 4.8 shows the point system used to rank waiting patients that was in place as of early 2009. The patient's rank within each blood group is determined by the time the patient has been waiting and

---

the quality of HLA match with the donor, with additional points awarded to sensitized patients who have a negative crossmatch and anyone who has previously donated an organ and now requires a kidney transplant. Because of the particular needs of children (candidates younger than 18 years; see Chapter 16), they are given priority for kidneys from donors younger than 35 years.

TABLE 4.8 United Network for Organ Sharing (UNOS) Point System for Allocation of Deceased Donor Kidneys (2009)

Factor	Points	Condition
Time waiting*	1 for each year of waiting time	
Quality of HLA match 0-A, B, DR mismatch†	2	Zero DR mismatches
	1	One DR mismatch

Panel-reactive antibody (PRA)	4	>80% PRA and negative crossmatch
Pediatric recipient priority for donors younger than 35 years		
Organ donor[‡]	4	Expanded criteria donor longest waiting patient (see text)

[*] Defined from the time a patient is activated on the UNOS computer. In some regions, defined by time receiving dialysis.

[†] O-A-, B-, and DR-mismatched organs are involved in national mandatory sharing program if recipient is highly sensitized or local sharing program if recipient is unsensitized.

[‡] Previous living donor in need of a kidney transplant.

The point system has been adjusted several times based largely on ongoing analyses of the transplantation results reported to UNOS by the Scientific Registry for Transplant Recipients (SRTR). The HLA component of the local allocation algorithm has been the most frequently modified part of the scheme. The importance of matching in determining graft outcome is well established; the extent to which matching should determine local kidney distribution remains controversial. Points for HLA-A matches were dropped in 1990 after analyses showed no survival benefit for this category of matched patients. With growing concerns regarding racial equity in transplantation, the B-locus matching points were eliminated in 2003 and were replaced with 2 points for zero HLA-DR mismatches and 1 point for one DR mismatch.

The allocation system was originally designed in an attempt to balance fairness (the waiting-time component) with medical utility (HLA matching to improve survival). The waiting-time component can be considered simplistically as a “line for a bus”—first

come, first served—and the HLA component as a kind of lottery in which the matched patient is the winner. Much has changed over the years because of the wide gap between the supply and demand for kidneys that has resulted in a wait time for kidney transplant from several months to several years. Because each year of waiting provides 1 point, the algorithm in place as of 2009 is essentially a long waiting line with some component of lottery as reflected by the 2 points for DR matching.

Expanded Criteria Donors

The term *expanded criteria donor* (ECD) *kidney* is preferable to the term *marginal kidney* and, for the purpose of organ allocation, is defined as a kidney from a deceased donor older than 60 years or aged 50 to 59 years with two additional risk factors, including a history of hypertension, death as a result of cerebrovascular accident, or an elevated terminal serum creatinine. ECD kidneys, which account for about 15% of deceased donor kidneys, have, statistically, at least a 70% increased risk for failing within 2 years compared with standard criteria kidneys (expressed positively, this means that if a standard kidney has a 2-year graft survival of 88%, an ECD kidney has an estimated survival at 2 years of about 80%). In 2003, the allocation of ECD kidneys was changed in an effort to speed their placement in an appropriate recipient so as to reduce the cold ischemia time and discard rate. ECD kidneys are offered only to those patients who have agreed to accept them, who have been informed of the risk, and who understand that these kidneys are more likely to fail. ECD kidneys are allocated according to waiting time alone. As a result, it is possible to anticipate when patients are close to being allocated an ECD kidney and to ensure that they are prepared for the procedure. Appropriate candidates for ECD kidneys are discussed in Chapter 7.

Zero-Mismatch Kidneys and Paybacks

Until 2008, all zero A, B, DR mismatch kidneys (see Chapter 3) were involved in a mandatory national sharing program. The advantage of the program was that it offered the fortunate recipient of the well-matched organ the benefit of an anticipated improved outcome, and it permitted highly sensitized patients to be exposed to the opportunity of being matched with a kidney with a negative crossmatch. About 17% of kidneys were allocated through the zero-mismatch program.

When a zero-mismatch kidney was allocated to a patient in a nonlocal OPO, a “debt” was generated that the recipient OPO was required to “pay back” to the original OPO when the next appropriate kidney became available. The purpose of the payback rule was to protect OPOs from being constant organ “exporters.” The need to pay back kidneys, however, may come at the expense of local recipients. As a result, the mandatory zero-mismatch national sharing policy has been modified and as of 2009 will only apply nationally to sensitized recipients (panel reactive antibody >20%). Locally, unsensitized, zero-mismatch recipients will retain priority.

New Allocation Policies for Deceased Donor Kidneys

Since the first development of a national allocation policy, changes have been made in response to new realities but without addressing the fundamental questions, “What is the purpose of the allocation algorithm”? and “Does the algorithm serve its intended purpose”? As noted previously, the algorithm in place as of 2009 has become, de facto, a line for a bus, and makes minimal attempt to match the donor kidney with the most appropriate recipient or to maximize the potential benefit that a kidney can provide. For instance, a kidney from a young trauma victim that could potentially function for 30 years may be allocated to an elderly recipient with comorbidities that greatly limit that patient's life span; similarly, a kidney from an older donor that has an intrinsically limited functional life span may be offered to a young recipient who may have decades of life ahead. To address these questions, an in-depth review of allocation policies has been undertaken by UNOS (details of the process are available at http://www.unos.org). Using two decades of outcome data available at the SRTR and a statistical model to determine kidney allocation and outcome (KPSAM), the number of life-years that a transplant would add to a patient's life compared with remaining on dialysis (LYFT) can be calculated as follows:

LYFT = estimated survival after transplant - estimated survival on dialysis × 0.8

The dialysis years are discounted by a factor of 0.8 to reflect surveys among dialysis patients that indicate that a year spent on dialysis is valued less than a year free of dialysis. The LYFT term can then become one of the determinant allocation factors. LYFT is primarily a measure of utility in that it determines the estimated survival time that a recipient of a specific donor kidney may expect to receive compared with remaining on dialysis. The degree to which the LYFT score will be used in allocation policy has yet to be determined. Concern has been raised that the LYFT concept is complex and that its inclusion may unfairly disadvantage older patients. Other potential allocation algorithms that match donor and recipient age raise similar concerns.

Another problem with the conventional algorithm is that it presumes, simplistically, that deceased donor kidneys come from either an ECD or nonECD source. Clearly the quality of an organ is a continuous variable. To address this issue, a donor profile index (DPI) has been developed that provides a continuous measure of organ quality based on readily available clinical information, including age, cause of death, presence of diabetes or hypertension, and renal function at the time of recovery. The DPI, or some modification of it, may become part of the allocation algorithm.

In the current algorithm, waiting time is determined by the date a potential recipient is listed on the UNOS waitlist. In any future allocation algorithm, the time spent waiting on dialysis will likely determine waiting time (preemptively listed patients can begin their wait when their estimated GFR is less than 20 mL per minute). Using dialysis time as waiting time is more equitable because it

does not penalize patients whose listing is delayed for reasons beyond their control. The percentage of panel reactive antibodies calculated by the frequency of unacceptable antigens will continue to be used in allocation policy.

Selected Readings

Chang GJ, Mahanty HD, Ascher N, et al. Expanding the donor pool: can the Spanish model work in the United States? Am J Transplant 2003:3:1259-1263.

Delmonico FL, Burdick J. Maximizing the success of transplantation with kidneys from older donors. N Engl J Med 2006;354:411-413.

Freeman R. Survival benefit: quality versus quantity and trade-offs in developing new renal allocation systems. Personal viewpoint. Am J Transplant 2007;7:1043-1046.

Frei U, Noeldeke J, Machold-Fabrizii V, et al. Prospective age-matching in elderly kidney transplant recipients: a 5-year analysis of the Eurotransplant Senior Program. Am J Transplant 2008;8:50-57.

Kutsogiannis A, Demetrios J., Pagliarello, et al. Medical management to optimize donor organ potential: review of the literature. Can J Anesth 2006;53:820-830.

Leichtman AB, Cohen D, Keith D, et al. Kidney and pancreas transplantation in the United States, 1997-2006: the HRSA Breakthrough Collaborative and the 58 DSA Challenge. Am J Transplant 2008;8(Pt 2):946-947.

Locke JE, Segev DL, Warren DS, et al. Outcomes of kidneys from donors after cardiac death: implications for allocation and preservation. Am J Transplant 2007;7:1797.

Luskin RS, Delmonico FL. Assessing organ donation from the dead should not be done by reporting a census of the living. Am J Transplant 2003;3:1185-1187.

Marks WH, Wagner D, Pearson TC, et al. Organ donation and utilization, 1995-2004: entering the collaborative era. Am J Transplant 2006;6:1101-1110.

Matesanz R, Miranda B. A decade of continuous improvement in cadaveric organ donation: the Spanish Model. J Nephrol 2002;15:22-28.

McDiarmid S, Pruett T, Graham W. The oversight of solid organ transplantation in the United States. Am J Transplant 2008;8:739-744.

Merion RM, Ashby VB, Wolfe RA, et al. Deceased-donor characteristics and the survival benefit of kidney transplantation. JAMA 2005;294:2726.

Moers C, Smits J, Maathius M, et al. Machine perfusion or cold storage in deceased-donor kidney transplantation. N Engl J Med 2009;360:7-19.

O'Connor KJ, Delmonico FL. Increasing the supply of kidneys for transplantation. Semin Dialysis 2005;18:460-462.

Roels L, Cohen B, Gachet C. Countries' donation performance in perspective: time for more accurate comparative methodologies. Am J Transplant 2007;7:1439-1443.

Rosendale JD, Kauffman MH, McBride M, et al. Aggressive pharmacologic donor management results in more transplanted organs. Transplantation 2003;75:482.

Rosengard BR, Feng S, Alfrey EJ, et al. Report of the Crystal City meeting to maximize the use of organs recovered from the cadaver donor. Meeting report. Am J Transplant 2002;2:701-711.

Saidi RF, Elias N, Kawai T, et al. Outcome of kidney transplantation using expanded criteria donors and donation after cardiac death kidneys: realities and costs. Am J Transplant 2007;7:2769-2774.

Sheehy E, Conrad SL, Brigham LE, et al. Estimating the number of potential organ donors in the United States. N Engl J Med 2003;349:667-674.

Steinbrook R. Organ donation after cardiac death. N Engl J Med 2007;357:209-213.

Sung RS, Galloway J, Tuttle-Newhall J, et al. Organ donation and utilization in the United States 1997-2006. Am J Transplant 2008;8(Pt 2):922-934.

Sung RS, Guidinger MK, Leichtman AB, et al. Impact of the expanded criteria donor allocation system on candidates for and recipients of ECD kidneys. Transplantation 2007;84:1138.

Wijdicks E. The diagnosis of brain death. N Engl J Med 2001;344;1215-1221.

Wood KE, Becker BN, McCartney JG, et al. Care of the potential organ donor. N Engl J Med 2004;351:2730.

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

5

Immunosuppressive Medications and Protocols for Kidney Transplantation

Gabriel M. Danovitch

A BRIEF HISTORY OF TRANSPLANT IMMUNOSUPPRESSION

To understand the construction of the immunosuppressive protocol and the use of immunosuppressive medications according to current standard transplantation practice, it helps to follow the development of organ transplantation and, in particular, kidney transplantation, since the 1950s. Although sporadic attempts at kidney transplantation had been made throughout the first half of the 20th century, the current era of transplantation was pioneered in the mid-1950s with live donor transplants from identical twins. The first attempts at immunosuppression used total-body irradiation; azathioprine was introduced in the early 1960s and was soon routinely accompanied by prednisolone. The polyclonal antibody preparations antithymocyte globulin (ATG) and antilymphocyte globulin (ALG) became available in the mid-1970s. With azathioprine and prednisolone as the baseline regimen and ATG or ALG used for induction or for the treatment of steroid-resistant rejection, the success rate of kidney transplantation was about 50% at 1 year, and the mortality rate was typically 10% to 20%.

The situation was transformed in the early 1980s with the introduction of cyclosporine. Because the results of kidney transplantation were poor, it was not hard to recognize the dramatic benefit of cyclosporine that produced statistically significant improvement in graft survival rates to greater than 80% at 1 year. Mortality rates decreased with more effective immunosuppression, reduced use of corticosteroids, and overall improvements in surgical and medical care. The standard immunosuppressive regimen consisted of cyclosporine and prednisone, often combined with azathioprine, now used as an adjunctive agent in what was called *triple therapy*. Although the benefits of cyclosporine were clearcut, its capacity to produce both acute and chronic nephrotoxicity was soon recognized to be a major detriment. In 1985, OKT3, the first monoclonal antibody used in clinical medicine, was introduced based on its capacity to treat first acute rejection episodes, although the toxicity of the drug tended to restrict its use to episodes of rejection that were resistant to high-dose steroids and, in some

programs, to use as an induction agent. With this limited armamentarium of medications—cyclosporine, azathioprine, corticosteroids, and the antibody preparations—the transplantation community entered the 1990s, achieving, with justifiable pride, success rates of up to 90% in many centers and minimal mortality. Because the number of available immunosuppressive medications was small, there was relatively little variation among the protocol options used in different programs.

Two major developments then followed. Tacrolimus was introduced into liver transplantation and eventually into kidney transplantation as an alternative to cyclosporine because of its capacity to produce equivalent patient and graft survival, and mycophenolate mofetil (MMF) was found to be a more effective agent than azathioprine by virtue of its capacity to reduce the incidence of acute rejection episodes when used with cyclosporine (and later with tacrolimus) and corticosteroids. Basiliximab and daclizumab, two humanized

---

monoclonal antibodies, were approved for use after kidney transplantation, also based on their capacity to reduce the incidence of acute rejection episodes, and a polyclonal antibody, Thymoglobulin, available in Europe for several years, was approved for use in the United States for the treatment of acute rejection.

The last major new drug made available for clinical immunosuppression was sirolimus, introduced in 1999 (a similar drug, everolimus, was later introduced in Europe). As of 2009, studies are in progress to evaluate several new chemical and biologic agents. The therapeutic armamentarium for transplant immunosuppression thus has continued to broaden and become more complex, as has the variety of potential drug combinations or protocols. To address this complexity, this chapter is divided into five sections. Part I reviews the drugs in current clinical use, emphasizing cyclosporine, tacrolimus, MMF, and sirolimus. Part II reviews the currently available biologic agents approved for use in transplantation. Part III discusses the clinical trial process used to develop new immunosuppressive agents and reviews available data on promising new agents at different stages of development. Part IV discusses combinations of these drugs in the form of clinically applied immunosuppressive protocols, both conventional and innovative. Part V discusses the treatment of the various forms of kidney transplant rejection.

PART I. IMMUNOSUPPRESSIVE AGENTS IN CURRENT CLINICAL USE

MECHANISM OF ACTION OF IMMUNOSUPPRESSIVE DRUGS: THE THREE-SIGNAL MODEL

The molecular mechanisms that are the target of immunosuppressive drugs are discussed in detail in Chapter 2. The three-signal model of T-cell activation and

subsequent cellular proliferation, illustrated in Plate 5.1, is a valuable tool for understanding the sites of action of the agents discussed below. In brief, *signal 1* is an antigen-specific signal provided by the triggering of the T-cell receptors by antigen-presenting cells (APCs) and is transduced through the CD3 complex. *Signal 2* is a non-antigen-specific costimulatory signal provided by the engagement

of B7 on the APC with CD28 on the T cell. These two signals activate the intracellular pathways that lead to the expression of interleukin-2 (IL-2) and other growth-promoting cytokines. Stimulation of the IL-2 receptor (CD25) leads to activation of mTOR (mammalian target of rapamycin) and provides *signal 3,* which triggers cell proliferation. As each of the immunosuppressive agents is discussed below, it is useful to refer to Plate 5.1 to review their relative sites of action.

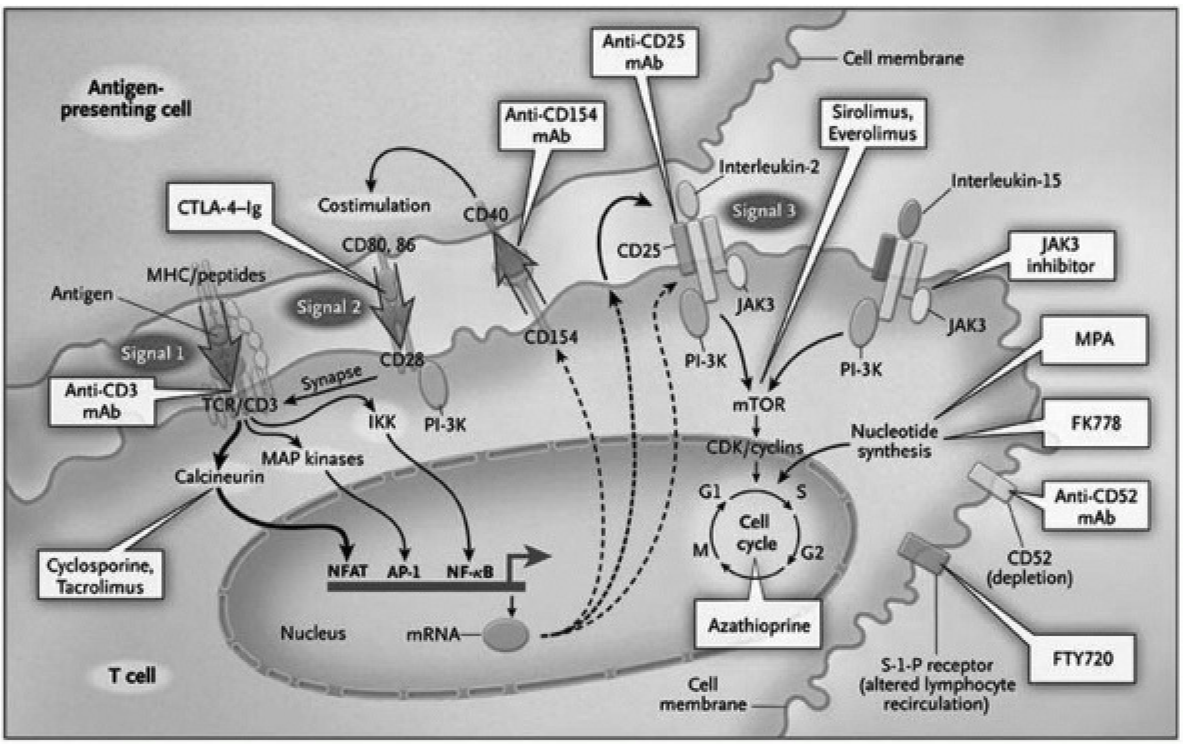


PLATE 5.1 Anti-CD154 antibody, FTY720, and FK778 have been withdrawn from clinical trials. MPA, mycophenolic acid. (From Halloran P. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2005;351:2715-2729, with permission. see color image)

Calcineurin Inhibitors: Cyclosporine and Tacrolimus

The term *calcineurin inhibitors* is useful because it emphasizes the similarity in the mechanism of action of the two drugs, *cyclosporine* and *tacrolimus,* which have served as the backbone of solid-organ transplant immunosuppression for the past 20 years. Although they are biochemically distinct, they are remarkably similar, not only in their

mechanism of action, but also in their clinical efficacy and side-effect profile. They are, therefore, considered together; discrete differences between them are discussed in the text and summarized in Table 5.1. The choice of agent is discussed in Part IV.

Cyclosporine is a small cyclic polypeptide of fungal origin. It consists of 11 amino acids and has a molecular weight of 1203. It is neutral and insoluble in water but soluble in organic solvents and lipids. The amino acids at positions 11, 1, 2, and 3 form the active immunosuppressive site, and the cyclic structure of the drug is necessary for its immunosuppressive effect. Tacrolimus, still often called by its nickname *Eff-Kay* from its laboratory designation *FK506,* is a macrolide antibiotic compound isolated from *Streptomyces tsukubaensis*.

Mechanism of Action

The calcineurin inhibitors differ from their predecessor immunosuppressive drugs by virtue of their selective inhibition of the immune response. They do not inhibit neutrophilic phagocytic activity as corticosteroids do, nor are they myelosuppressive. Cell surface events and antigen recognition also remain intact (see Chapter 2). Their immunosuppressive effect depends on the formation of a complex with their cytoplasmic receptor proteins, *cyclophilin* for cyclosporine and tacrolimus-binding protein (*FKBP*) for tacrolimus (Plate 5.1). This complex binds with *calcineurin,* whose normal function is to act as a phosphatase that dephosphorylates certain nuclear regulatory proteins (e.g., *nuclear factor of activated T cells*) and hence facilitates their passage through the nuclear membrane (see Chapter 2 and Fig. 2.5). Inhibition of calcineurin thereby impairs the expression of several critical cytokine genes that promote T-cell activation, including those for IL-2, IL-4, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). The transcription of other genes, such as CD40 ligand and the proto-oncogenes H-*ras* and c-*myc,* is also impaired. The importance of these factors in T-cell activation is discussed in more detail in Chapter 2, but as a result of calcineurin inhibition, there is a quantitative limitation of cytokine production and downstream lymphocyte proliferation.

Cyclosporine enhances the expression of transforming growth factor-β (TGF-β), which also inhibits IL-2 and the generation of cytotoxic T lymphocytes, and may be responsible for the development of interstitial fibrosis, an important feature of calcineurin inhibitor nephrotoxicity. TGF-β has also been implicated as an important factor in the proliferation of tumor cells, which may be relevant to the course of certain post-transplantation neoplasias (see Chapter 10). The *in vivo* effects of cyclosporine are blocked by anti-TGF-β, indicating that TGF-β may be central to the mediation of both the beneficial and detrimental effects of the calcineurin inhibitors.

Patients receiving successful calcineurin inhibitor-based immunosuppression maintain a degree of immune responsiveness that is still sufficient to

---

maintain host defenses. This relative immunosuppression may be a reflection of the

fact that at therapeutic levels of these drugs, calcineurin activity is reduced by only about 50%, permitting strong signals to trigger cytokine expression and generate an effective immune response. In stable patients receiving cyclosporine, CD4+ T cells have reduced IL-2 production to a degree that is inversely correlated to drug levels. The degree of inhibition of calcineurin activity and IL-2 production may be at the fulcrum of the delicate balance that exists between too much and too little immunosuppression.

TABLE 5.1 Some Comparative Features of Cyclosporine and Tacrolimus

Feature	Cyclosporine	Tacrolimus
Mode of action	Inhibition of calcineurin	Inhibition of calcineurin
Daily maintenance dose	About 3-5 mg/kg	About 0.15-0.3 mg/kg
Administration	PO and IV	PO and IV*
Absorption bile dependent	Sandimmune, yes; Neoral, no	No
Oral dose available (capsules)	100 mg; 25 mg	5 mg; 1 mg; 0.5 mg
Drug interactions	Similar	Similar

Capacity to prevent rejection	+	++?
Use with MMF	+	+[b]
Use with sirolimus	+[c]	+[c]
Nephrotoxicity	+	+
Steroid sparing	+	++?
Hypertension and sodium retention	++	+
Pancreatic islet toxicity	+	++
Neurotoxicity	+	++
Hirsutism	+	-
Hair loss	-	+

Gum hypertrophy	+	-
Gastrointestinal side effects	-	+
Gastric motility	-	+
Hyperkalemia	+	+
Hypomagnesemia	+	+
Hypercholesterolemia	+	-
Hyperuricemia, gout	++	+

-, No or little effect; +, known effect; ++, effect more pronounced; ++?, probable greater effect; IV, intravenous; MMF, mycophenolate mofetil; PO; by mouth.

* IV rarely needed because oral absorption is good.

† Dose of MMF may be less when used with tacrolimus.

‡ Nephrotoxicity may be exaggerated when used in full dose.

Data are based on available literature and clinical experience.

Formulations and Pharmacokinetics

Cyclosporine. The original formulation of cyclosporine, the oil-based Sandimmune, has largely been replaced by the microemulsion formulation, Neoral. Both formulations are available in two forms: a 100-mg/mL solution that is drawn up by the patient into a graduated syringe and dispensed into orange juice or milk, and 25-mg and 100-mg soft-gelatin capsules. Patients usually prefer the convenience of the capsule that is typically administered twice daily.

The absorption of cyclosporine after an oral dose can be represented graphically in the form of a concentration-time curve (Fig 5.1). The time to peak concentration of Sandimmune cyclosporine (*tmax*) is variable but averages 4 hours. A substantial proportion of transplant recipients exhibit a second peak. The bioavailability of Neoral (*F*) is better than that of Sandimmune, and there is less variability in cyclosporine pharmacokinetics. Peak cyclosporine levels (*Cmax*) of Neoral cyclosporine are higher, and the trough concentration (*Cmin*) correlates better with the systemic exposure, as reflected by the *area under the curve* (AUC).

The improved gastrointestinal (GI) absorption of the microemulsion and lesser dependence on bile for absorption may reduce the necessity for intravenous cyclosporine administration. Compared with intravenous infusion, the bioavailability of the orally administered drug is in the range of 30% to 45%. Conversion between the oral and intravenous forms of the drug perioperatively requires a 3:1 dose ratio. Bioavailability of oral cyclosporine increases with time, possibly as a result of improved absorption by the previously uremic GI tract. As a result, the amount of cyclosporine required to achieve a given blood level tends to fall with time and typically reaches a steady level within 4 to 8 weeks. Food tends to enhance the absorption of cyclosporine (see Chapter 19).

The development of generic formulations of cyclosporine and other immunosuppressive agents is controversial because of the critical importance of these drugs to the success of transplantation and the corporate and financial implications of their introduction. Cyclosporine is regarded as a drug with a *narrow therapeutic index*, and the standards for proving the *bioequivalence* of generic forms are more rigorous. Generic drugs, however, do not undergo the same extensive evaluation required of new drugs, and information on discrete differences in their pharmacokinetics in different ethnic groups is not available. Generic formulations of cyclosporine, such as the capsule *cyclosporine USP* (Eon Labs) and the capsule *Gengraf*, are in widespread use in the United States; other generic formulations are available outside of the United States. The

generic formulations are generally claimed to have an absorption profile that is very similar to that of Neoral. The capsules have received a so-called AB rating by the U.S. Food and Drug Administration (FDA), which means that they may be substituted for Neoral cyclosporine without the approval of the prescriber. If generic formulations are used, it is probably better to use them consistently and to avoid switching formulations. If conversions are made between the different formulations, it is wise to monitor drug levels and renal function (see Part IV). Extensive experience with generic formulations of cyclosporine has not demonstrated them to be inferior to the brand drug.

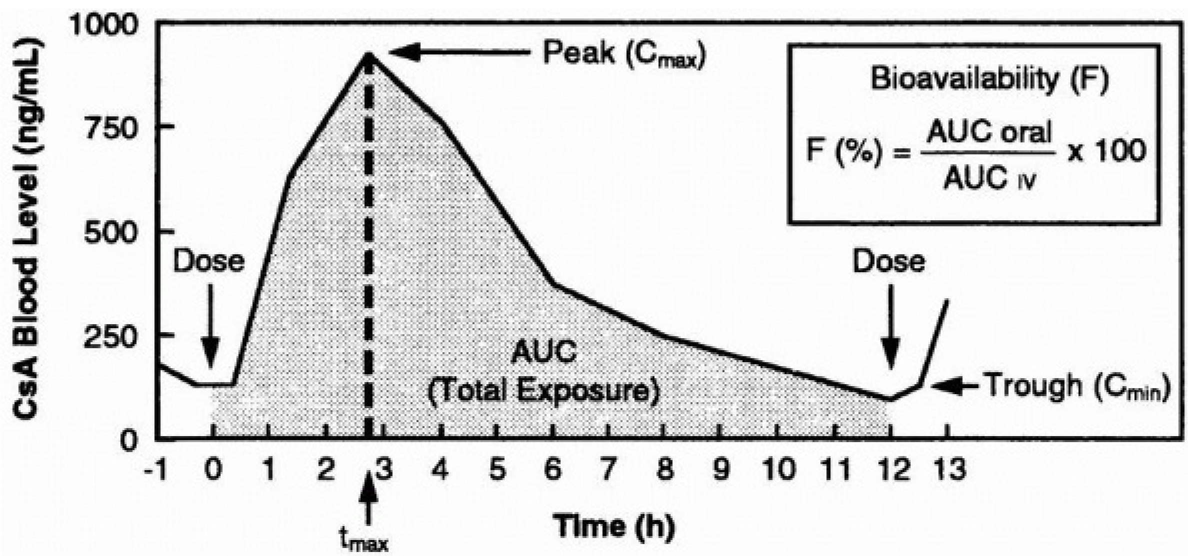


FIGURE 5.1 Cyclosporine pharmacokinetic profile. AUC, the area under the concentration-time curve, which approximates a patient's total exposure to cyclosporine over a dosage interval; Cmax, the maximum cyclosporine concentration; Cmin, the minimum cyclosporine concentration, or trough level; F, percentage bioavailability of orally administered cyclosporine over a dosage interval; tmax, the time to reach maximum cyclosporine concentration. (From Grevel J, Kahan BD. Area under the curve monitoring of cyclosporine therapy: the early posttransplant period. Ther Drug Monit 1991;13:89-95, with permission.)

Tacrolimus. Tacrolimus (Prograf) is available in an intravenous formulation and as 5-mg, 1-mg, and 0.5-mg capsules. It is typically administered twice daily. A long-acting once-daily formulation (Advagraf) is available in Europe but not in the United states. GI absorption is independent of bile salts. Because of the effectiveness and relative consistency of its absorption, it is rarely necessary to use the intravenous formulation, and if necessary, the drug can be administered through a nasogastric tube. It is absorbed primarily from the small intestine, and its oral bioavailability is about 25%, with large interpatient and intrapatient variability, particularly for patients with GI disease. Gastric emptying of solids is faster in patients taking tacrolimus than in those

receiving cyclosporine, a property that may be beneficial for patients with gastric motility disorders. Diarrhea may lead to increased absorption of tacrolimus from the lower GI tract with resultant toxic levels. Generic formulations of tacrolimus are being developed, but as of early 2009, they are not available in the United States. When available, their safety and effectiveness will need to be evaluated with great care.

Distribution and Metabolism

In the blood, one third of absorbed and infused cyclosporine is found in plasma, bound primarily to lipoproteins. Most of the remaining drug is bound to erythrocytes. Whole-blood drug levels (see “Drug Level Monitoring,” below) are thus typically threefold higher than plasma levels. The binding of cyclosporine to lipoproteins may be important in the transfer of the drug through plasma membranes, and the toxic effects of cyclosporine may be exaggerated by low cholesterol levels and reduced by high cholesterol levels. The binding of cyclosporine to the low-density lipoprotein receptor may account for the hyper-lipidemia associated with its use.

Tacrolimus also has a high affinity for formed blood elements, but it differs from cyclosporine in that, although it is highly protein bound, it is not significantly associated with lipoproteins, and it has a less unfavorable effect on the cholesterol level than does cyclosporine. Both parent drugs have a half-life of about 8 hours and are metabolized to multiple metabolites by the cytochrome P-450 IIIA (CYP3A) found in the GI and liver microsomal enzyme systems. GI metabolism through CYP3A and *p*-glycoprotein produces a so-called first-pass metabolism, and the heterogeneity in intestinal CYP3A gene expression may explain some of the wide interpatient variability in drug kinetics. The liver is often considered the most important site of drug metabolism, but GI metabolism may account for up to half of cyclosporine metabolism. Gut metabolism of tacrolimus is also extensive. Some of the drug metabolites may have immunosuppressive and nephrotoxic potential, and the plasma levels of the most important cyclosporine metabolite, M17, may be similar to that of the parent compound. Because both drugs are excreted in the bile with minimal renal excretion, drug doses do not need to be modified in the presence of kidney dysfunction. Neither drug is significantly dialyzed, and either can be administered during dialysis treatment without dose adjustment. The pharmacokinetic

---

parameters of both drugs may vary among patient groups, and these variations may have clinical consequences. Pediatric and African American transplant recipients may require relatively larger doses and short dosage intervals. Longer dosage intervals may be required in older patients and in the presence of liver disease.

Drug-Level Monitoring

The measurement of cyclosporine and tacrolimus levels is an intrinsic part of the management of transplant patients because of variation in interpatient and

intrapatient metabolism. There is also a relationship, albeit an inconsistent one, between blood levels of the drug and episodes of rejection and toxicity. Drug-level monitoring is the source of much confusion because of the various assays available and the option of using different matrices (i.e., plasma or whole blood) for their measurement.

When Sandimmune was introduced, the trough level of cyclosporine (drawn immediately preceding the next dose), rather than the peak level, was measured because its timing was more consistent and appeared to correlate better with toxic complications. More sophisticated techniques of monitoring were suggested whereby a full, or abbreviated, pharmacokinetic profile is constructed to calculate the AUC, which reflects the bioavailability of the drug and may theoretically allow for more precise and individualized patient management. Although attractive, these techniques never proved popular because of their cost and inconvenience.

Evidence suggests that because of the more consistent absorption of Neoral cyclosporine, its peak level (typically 2 hours after dosing; Fig. 5.1) may correlate better with drug exposure and clinical events than the trough level. So-called C2 monitoring is applied routinely in some centers and clinical trials. For tacrolimus, the trough level is used for monitoring, and this level is an adequate approximation of drug exposure. Recommendations for target blood levels at different stages after transplantation are discussed in Part IV.

Cyclosporine concentrations can be measured in plasma or whole blood. Whole blood (ethylenediaminetetraacetic acid [EDTA] anticoagulated) is the recommended specimen type because the distribution of cyclosporine between plasma and erythrocytes is temperature dependent. The clinician cannot begin to assess the significance of a cyclosporine level without knowing what kind of assay is being used. Several methods are currently available to measure cyclosporine, and each differs in specificity for parent compound. *High-performance liquid chromatography* (HPLC) is the most specific method for measuring unmetabolized parent cyclosporine and is considered the reference method. HPLC, however, is expensive and labor intensive and is not available at all centers. Immunoassays, which use monoclonal antibodies against cyclosporine, are commonly used and have largely replaced HPLC because they can be performed on automated chemistry analyzers. The most commonly used immunoassay to measure cyclosporine in whole-blood samples is the Abbott (Chicago, IL) fluorescence polarization immunoassay (FPIA), which has significant cross-reactivity with cyclosporine metabolites and overestimates cyclosporine by as much as 45%. Samples for quantitation of peak cyclosporine levels should be clearly identified when sent to the laboratory and should be reported as such. These samples may exceed the linearity of the assay and will need to be diluted for accurate quantitation. For monitoring of tacrolimus concentrations, most laboratories use the Abbott monoclonal antibody-based *microparticle enzyme immunoassay* (MEIA) that can be performed on an automated instrument (IMx). This assay permits accurate estimation of tacrolimus levels as low as 2 ng/mL. Abbott has also developed a *chemiluminescent microparticle*

immunoassay (CMIA) that is available on the

ARCHITECT family of instruments with a reported detection limit of less than 1 ng/mL. Target cyclosporine (peak and trough) and tacrolimus (trough) levels are discussed in the section on immunosuppressive protocols.

Drug Interactions

The interaction of the calcineurin inhibitors with many commonly used drugs demands constant attention to drug regimens and cognizance of potential interactions. New drugs should be introduced with care, and patients should be warned to consult drug package inserts and physicians familiar with the use of cyclosporine and tacrolimus before considering new pharmacologic therapy. Some of the drug interactions discussed below are consistent and well established (and are emphasized in **bold** lettering); others have been described in small series and case reports or are anticipated based on the pharmacologic properties of the agents. Any drug that impacts on P-450 activity in the liver or intestinal tract, or that interacts with a drug that does, should be regarded as having a potential interaction with the calcineurin inhibitors. Some drugs affect calcineurin inhibitor levels when administered orally, but not intravenously, because the drug interaction is taking place at the intestine. In addition to their affect on P-450, the calcineurin inhibitors inhibit multidrug resistance protein (MDR), and many of the interactions thought to be due to P-450 are, in fact, due to an effect on MDR. The possibility that the calcineurin inhibitor is affecting the blood level of the interacting drug should also be considered. Unless a comment is made to the contrary, the drug interactions noted below are common to both cyclosporine and tacrolimus, although more have been described with cyclosporine, which has been available longer. Drug interactions between calcineurin inhibitors and other immunosuppressive drugs are discussed in Part IV. Interactions with antibiotics are discussed below and in Chapter 11. Interactions with food are discussed in Chapter 19. Interactions with psychotropic drugs are discussed in more detail in Chapter 17. Drugs that cause impairment of graft function by virtue of their nephrotoxicity alone are not specifically discussed here. *It should be emphasized that the sections below are not intended to represent a complete listing of all reported and potential drug interactions.*

Drugs that Decrease Calcineurin Inhibitor Concentration by Induction of P-450 Activity. *Antituberculous Drugs.* **Rifampin** (and **rifabutin** to a lesser extent) markedly reduces cyclosporine and tacrolimus levels, and it may be difficult to achieve therapeutic levels for patients taking rifampin, the use of which should be avoided if at all possible. Pyrazinamide and ethambutol may reduce drug levels, and their use requires monitoring. Isoniazid (INH) can be used with careful drug-level monitoring and is the preferred drug for tuberculosis prophylaxis if this proves essential (see Chapter 11).

Anticonvulsants. Of the so-called first-generation antiepileptic drugs, **barbiturates**

markedly reduce cyclosporine and tacrolimus levels. Dose requirements may double or triple, and thrice-daily administration may be required under careful supervision. **Phenytoin** and primidone reduce levels and should be used with great care. The average requirement for cyclosporine or tacrolimus is about doubled for patients receiving phenytoin. **Carbamazepine** may also decrease cyclosporine levels, but the effect is less pronounced. Benzodiazepines and valproic acid do not affect drug levels, but the latter drug has been associated with hepatotoxicity. Modafinil can cause an up to 50% reduction in calcineurin inhibitor levels. Patients taking these anticonvulsants before transplantation should have a neurologic assessment with a view toward discontinuing them

---

when possible or exchanging them for one of the new generation of anticonvulsants that do not interact with calcineurin inhibitors.

Of the second generation antiepileptic drugs, oxcarbazepine (Trileptal) may decrease cyclosporine levels. Gabapentin (Neurontin) and levetiracetam (Keppra) and other drugs in this category do not appear to have significant interactions.

Other Drugs. There are isolated reports of several antibiotics, including nafcillin, intravenous trimethoprim, intravenous sulfadimidine, imipenem, cephalosporins, and terbinafine, reducing cyclosporine level. An increased incidence of acute rejection episodes has been described after the introduction of ciprofloxacin. The antidepressant herbal preparation *Hypericum perforatum* (St. John's wort) may reduce cyclosporine levels by enzyme induction. Ticlopidine may reduce cyclosporine levels. Cholestyramine, GoLYTELY, sevelamer (Renagel), and olestra may reduce levels by impairing GI absorption. Corticosteroids are inducers of P-450, an effect that needs to be considered if their administration is discontinued. Following cessation of concomitant corticosteroid therapy, tacrolimus levels may increase by up to 25%. The serum creatinine level may increase as a result and lead to a confusing clinical picture.

Prolonged Use. If prolonged use of a drug that induces P-450 activity is required, addition of a drug that inhibits or competes with the P-450 system (e.g., **diltiazem, ketoconazole)** may facilitate the achievement of therapeutic calcineurin inhibitor levels. Administration of the calcineurin inhibitor on a thrice-daily basis rather than the usual twice-daily basis may also be effective.

Drugs that Increase Calcineurin Inhibitor Levels by Inhibition of P-450 or by Competition for Its Pathways. *Calcium Channel Blockers*. **Verapamil, diltiazem, amlodipine,** and **nicardipine** may significantly increase calcineurin inhibitor levels. Diltiazem and verapamil are sometimes added routinely as adjuncts to the immunosuppressive regimen. Their use may safely permit up to a 40% reduction in the cyclosporine dose. Careful monitoring of drug levels is required when these calcium channel blockers are used for the management of hypertension or heart disease, and physicians and their patients should be specifically warned that changing the dosage of these drugs is equivalent to changing the dosage of the calcineurin inhibitor. Brand-

name and generic forms of these drugs (e.g., Cardizem, Dilacor, Tiazac, and Cartia are all forms of diltiazem) may have different effects on calcineurin inhibitor levels. Nifedipine, isradipine, and felodipine have similar hemodynamic effects but have minimal effects on drug levels.

Antifungal Agents. **Ketoconazole, fluconazole, itraconazole,** and **voriconazole** markedly elevate calcineurin inhibitor levels. The interaction with ketoconazole is a particularly potent one, which may permit a safe reduction of up to 80% in the cyclosporine or tacrolimus dose. Great care must be taken when stopping and starting these antifungal agents. An important interaction between ketoconazole and histamine blockers has also been described. The effective reabsorption of ketoconazole from the GI tract requires acidic gastric contents, and the addition of a histamine-2 receptor antagonist may reduce its absorption, indirectly producing a clinically significant fall in calcineurin inhibitor levels.

Antibiotics. **Erythromycin,** even in low doses, may increase calcineurin inhibitor levels. Other macrolide antibiotics (e.g., clarithromycin, josamycin, ponsinomycin) may also increase levels. There are conflicting reports on the impact of

---

azithromycin on drug levels; however, this drug can generally be given in short courses without monitoring. Because erythromycin is prescribed so ubiquitously, physicians, dentists, and patients should be warned about this interaction. Chloramphenicol may increase tacrolimus levels.

Antiretroviral Therapy. With the advent of highly active antiretroviral therapy (HAART), selected HIV-positive patients may be deemed candidates for kidney transplantation (see Chapters 7 and 11). Some of the antiretroviral agents, particularly protease inhibitors, are potent inhibitors of P-450. **Ritonavir** is the most potent inhibitor of P-450 that is clinically available, and when used alone or in combination (kaletra-retonavir/lopinavir), very small doses of calcineurin inhibitor (e.g., 1 mg/week of tacrolimus) may maintain adequate drug levels. Tenofovir (a component of Truvada and Atrypla) is nephrotoxic and should be avoided after transplantation. Because of multiple drug-drug interactions, immunosuppressive management of HIV-positive patients requires a close and ongoing collaboration and coordination between infectious disease consultants and the transplantation team.

Histamine Blockers. There are conflicting reports regarding the use of cimeti-dine, ranitidine, and omeprazole with calcineurin inhibitors. These drugs may increase creatinine levels without reducing the glomerular filtration rate (GFR) by suppressing proximal tubular creatinine secretion. There may be increased hepatotoxicity when ranitidine and cyclosporine are used in combination.

Hormones. Corticosteroids in high and low doses may decrease the clearance of cyclosporine metabolites. This effect may be particularly pronounced during “pulse” steroid therapy and may result in a confusing clinical picture if the drug levels are measured by a nonspecific assay. Oral contraceptives, anabolic steroids, testosterone,

norethisterone, danazol, and somatostatin may also increase drug levels.

Other Drugs. Amiodarone, carvedilol, allopurinol, bromocriptine, and chloro-quine are reported to increase cyclosporine levels. Metoclopramide and grapefruit juice increase the absorption of calcineurin inhibitors (see Chapter 18).

Drugs that May Exaggerate Calcineurin Inhibitor Nephrotoxicity. Any potentially nephrotoxic drug should be used with caution in combination with the calcineurin inhibitors because the vasoconstrictive effect of the drug tends to potentiate other nephrotoxic mechanisms. Well-substantiated enhanced renal impairment has been described after the introduction of **amphotericin** and **aminoglycosides,** and renal impairment may occur earlier than anticipated. **Nonsteroidal antiinflammatory drugs** should be avoided if possible but can be given for short periods under supervision. Calcineurin inhibitors may potentiate the hemodynamic renal dysfunction seen with **angiotensin-converting enzyme inhibitors** and **angiotensin receptor antagonists.** Metoclopramide may increase calcineurin inhibitor levels by increasing its intestinal reabsorption. A syndrome of diarrhea, hepatopathy, and renal dysfunction has been ascribed to the interaction between cyclosporine and colchicine, particularly when given to patients with familial Mediterranean fever.

Lipid-Lowering Agents. The β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (HCRIs) are frequent accompaniments of the immunosuppressive protocol (see Part IV). **Lovastatin** has been implicated in several cases of acute renal failure. When used in full doses in combination with cyclosporine, lovastatin can cause rhabdomyolysis with elevated creatine phosphokinase

---

levels and acute renal failure. Myopathy alone has been observed in up to 30% of recipients of the lovastatin-cyclosporine combination, with symptoms of muscle pain and tenderness developing 6 weeks to 16 months after commencement of therapy. The myopathic syndrome has not been observed when lova-statin is used in a daily dose of 20 mg or less. Even this dose should be used with caution, however, and patients should be made aware of the potential interaction. The coadministration of lovastatin with gemfibrozil further increases the likelihood of rhabdomyolysis. The newer HCRIs—pravastatin, fluvastatin, simvastatin, atorvastatin, rosuvastatin—should be introduced at low doses and maximal doses avoided. Cyclosporine may increase the levels of eze-timibe, but ezetimibe has not been reported to affect the levels of cyclosporine. Cholestyramine may interfere with cyclosporine absorption from the GI tract.

Side Effects

Nephrotoxicity. Nephrotoxicity is the major "thorn in the side" of these remarkable drugs. Theories linking the mechanism of immunosuppression and nephrotoxicity are discussed later. The terms *cyclosporine* and *FK toxicity* are often used loosely, and it is important to note that these terms encompass several distinct, overlapping syndromes (Table 5.2). Readers are referred to the extensive review of this topic by Naesens and

colleagues (see “Selected Readings”).

Functional Decrease in Renal Blood Flow and Filtration Rate. The calcineurin inhibitors produce a dose-related, reversible, renal vasoconstriction that particularly affects the afferent arteriole (Fig. 5.2). The glomerular capillary ultrafiltration coefficient (Kf) also decreases, possibly as a result of increased mesangial cell contractility. Most of the studies on the mechanism of this effect have used cyclosporine rather than tacrolimus. The picture is reminiscent of “prerenal” dysfunction, and in the acute phase, tubular function is intact.

The normal regulation of the glomerular microcirculation depends on a complex, hormonally mediated balance between vasoconstriction and vasodilation. Cyclosporine-induced vasoconstriction is caused, at least in part, by alteration of arachidonic acid metabolism in favor of the vasoconstrictor thromboxane. Cyclosporine is also a potential inducer of the powerful vasoconstrictor endothelin, and circulating endothelin levels are elevated in its presence. Cyclosporine-induced changes in glomerular hemodynamics can be reversed by specific endothelin inhibitors and by antiendothelin antibodies. The sympathetic nervous system is also activated.

TABLE 5.2 Syndromes of Calcineurin Inhibitor Nephrotoxicity
Exaggeration of early post-transplantation graft dysfunction
Acute reversible decrease in GFR
Acute microvascular disease
Chronic nonprogressive decrease in GFR
Chronic progressive decrease in GFR

Hypertension and electrolyte abnormalities

Sodium retention and edema

Hyperkalemia

Hypomagnesemia

Hyperchloremic acidosis

Hyperuricemia

GFR, glomerular filtration rate.

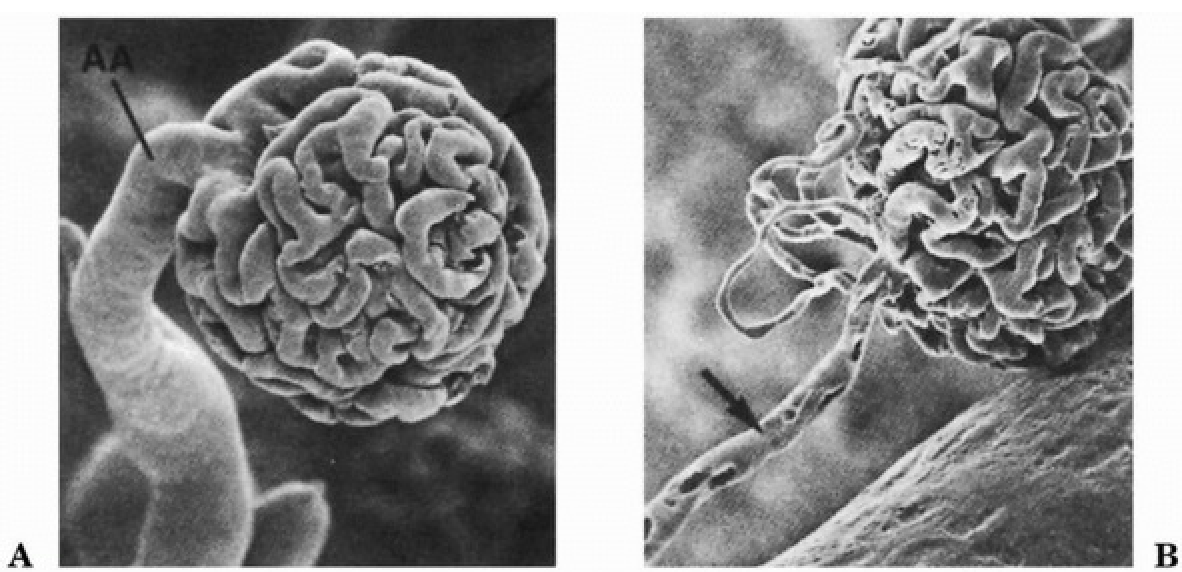


FIGURE 5.2 Cyclosporine-induced afferent arteriolar vasoconstriction. **A:** Control rat showing afferent arteriole (AA) and glomerular tuft. **B:** Constricted afferent arteriole *(arrow)* and glomerular tuft after 14 days of cyclosporine at 50 mg/kg per day. (From English J, Evan A, Houghton DC. Cyclosporine-induced acute renal dysfunction in the rat: evidence of arteriolar vasoconstriction with preservation of tubular function. Transplantation 1987;44:135-141, with permission.)

Several *in vivo* and *in vitro* studies have suggested that alterations in the L-arginine nitric oxide (NO) pathway may be involved in calcineurin-induced renal vasoconstriction. NO causes relaxation of preglomerular arteries and improves renal blood flow. The constitutive enzyme endothelial nitric oxide synthase (NOS) is produced by renal endothelial cells and modulates vascular tone. Both acute and chronic cyclosporine toxicity can be enhanced by NOS inhibition with *N*-nitro-L-arginine-methyl ester and ameliorated by supplementation with L-arginine. Interestingly, sildenafil (Viagra) increases GFR in transplant patients, presumably by reversing this effect.

Calcineurin inhibitor-induced renal vasoconstriction may manifest clinically as delayed recovery of early malfunctioning grafts or as a transient, reversible, dose-dependent, blood-level-dependent elevation in serum creatinine concentration that may be difficult to distinguish from other causes of graft dysfunction. Vasoconstriction may be a reversible component of chronic calcineurin inhibitor toxicity, which may amplify the functional severity of the chronic histologic changes seen with prolonged use. The vasoconstriction may be more pronounced with cyclosporine than with tacrolimus and also helps to account for the hypertension and the tendency for sodium retention that are commonly associated with cyclosporine use.

Chronic Interstitial Fibrosis. Interstitial fibrosis, which may be patchy or “striped” and associated with arteriolar lesions (see Chapter 14), is a common feature of long-term calcineurin inhibitor use. This lesion may produce chronic renal failure in recipients of organ transplants; however, several long-term studies show that in the dose regimens currently employed, kidney function may remain stable, although often impaired, for many years. The mechanism of calcineurin inhibitor-induced interstitial fibrosis remains poorly defined.

Evidence from experimental models suggests that chronic nephropathy involves an angiotensin-dependent up-regulation of molecules that are important in the scarring process, such as TGF-ß and osteopontin. Enhanced production of TGF-ß in normal T cells may provide the link between the immunosuppressive effects of the calcineurin inhibitors and their nephrotoxicity, and variation in fibrogenic gene expression may help explain the varying consistency of this

effect. Calcineurin-inhibitor induced hypomagnesemia may induce interstitial inflammation and enhance the production of TGF-ß, thereby perpetuating chronic

fibrotic lesions. Interstitial fibrosis may also be a reflection of intense and prolonged vasoconstriction of the renal microcirculation. Cyclosporine may also impair the regenerative capacity of microvascular endothelial cells and induce apoptosis. The resulting chronic renal ischemia may enhance the synthesis and accumulation of extracellular matrix proteins in the interstitium.

Acute Microvascular Disease. Thrombotic microangiopathy (TMA) (see Chapters 9 and 14) is a distinct form of calcineurin inhibitor vascular toxicity that may manifest as renal involvement alone or as a systemic illness. It produces a syndrome reminiscent of thrombotic thrombocytopenic purpura (TTP). In TTP, potentially pathogenic inhibitory antibodies against the von Willebrand factor (vWF)-cleaving protease ADAMTS13, a zinc metalloprotease, have been detected. A similar mechanism has been described in calcineurin inhibitor-induced TMA.

Electrolyte Abnormalities and Hypertension. Impaired sodium excretion is a reflection of the renal vasoconstrictive effect of the calcineurin inhibitors. Patients receiving long-term cyclosporine therapy tend to be hypertensive (see Chapter 10) and to retain fluid. Studies show activation of the renin-angiotensin-aldosterone system and sympathetic nervous system and suppression of atrial natriuretic factor, which results in attenuation of the natriuretic and diuretic response to an acute volume load. NO production is also impaired. Hypertension tends to be less marked (or the need for antihypertensive drugs may be less) for patients receiving tacrolimus, possibly because it produces less peripheral vasoconstriction than does cyclosporine.

Hyperkalemia is common and occasionally requires treatment, although it is rarely life-threatening as long as kidney function remains good. It is not uncommon for patients taking calcineurin inhibitors to have potassium levels in the mid-fives. Hyperkalemia is often associated with a mild *hyperchloremic acidosis* and an intact capacity to excrete acid urine. The clinical picture is thus reminiscent of type IV renal tubular acidosis. Patients receiving cyclosporine may have an impaired capacity to excrete an acute potassium load, and there is evidence to suggest impaired production of aldosterone, an acquired impaired renal response to its action, and inhibition of cortical collecting duct potassium secretory channels. Hyperkalemia may be exaggerated by concomitant administration of β blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. A defect of collecting tubule hydrogen ion secretion has been described with tacrolimus. Both drugs are magnesuric and hypercalciuric, and hypomagnesemia is commonly associated with their use. In liver transplantation, hypomagnesemia may predispose patients to seizures; this has been observed rarely in kidney recipients. The urinary loss of Ca^{2+} and Mg^{2+} is due to down-regulation of specific transport proteins. Magnesium supplements are often prescribed but may be ineffective because of a lowered renal magnesium threshold (see Chapter 19). Both cyclosporine and tacrolimus can produce hyperuricemia, although only cyclosporine has been associated with gout, which may resolve when cyclosporine is switched to tacrolimus.

Methods of Amelioration. The vexing issue of calcineurin inhibitor nephrotoxicity has spawned a variety of clinical and experimental approaches designed to modify the renal effects of these drugs, particularly their capacity to produce vasoconstriction. Low-dose dopamine is used in some centers in the early postoperative period to “encourage” urine output. Calcium channel blockers given to both the donor (see Chapter 4) and the recipient (see Part IV) may reduce

---

the incidence and severity of delayed graft function. Omega-3 fatty acids in the form of 6 g of fish oil each day were thought to increase renal blood flow and GFR by reversing the cyclosporine-induced imbalance between the synthesis of vasodilator and vasoconstrictor prostaglandins, but long-term studies have shown no such benefit. The prostaglandin agonist misoprostol and thromboxane synthetase inhibitors may have a similar effect. Various protocol adjustments, discussed later in this chapter, can also be employed to minimize calcineurin inhibitor toxicity.

Nonrenal Calcineurin Inhibitor Toxicity. *Gastrointestinal.* Episodes of hepatic dysfunction typically manifesting as subclinical, mild, self-limited, dose-dependent elevations of serum aminotransferase levels with mild hyperbilirubinemia may occur in nearly half of all kidney transplant recipients taking cyclosporine and occur less frequently in those taking tacrolimus. No specific hepatic histologic lesion has been described in humans, and the hyperbilirubinemia is a reflection of disturbed bile secretion rather than hepatocellular damage. Cyclosporine does not itself produce progressive liver disease; other causes, most frequently one of the viral hepatitides, need to be considered when this occurs. Cyclosporine therapy is associated with an increased incidence of cholelithiasis, presumably resulting from an increased lithogenicity of cyclosporine-containing bile. Varying degrees of anorexia, nausea, vomiting, diarrhea, and abdominal discomfort occur in up to 75% of patients receiving tacrolimus, and less frequently in patients receiving cyclosporine.

Cosmetic. The cosmetic complications of cyclosporine must be treated seriously, particularly in women and adolescents, because of the misery they can produce and the temptation to resolve them through noncompliant behavior. Cosmetic complications are often exaggerated by concomitant use of corticosteroids. They are less prominent for patients receiving tacrolimus.

Hypertrichosis in varying degrees occurs in nearly all patients receiving cyclosporine and is particularly obvious in dark-haired girls and women. A coarsening of facial features is observed in children and young adults, with thickening of the skin and prominence of the brow. Tacrolimus may produce hair loss and frank alopecia. Gingival hyperplasia, which can be severe, may develop in patients receiving cyclosporine and is exaggerated by poor dental hygiene and possibly by concomitant use of calcium channel blockers. Azithromycin, a macrolide antibiotic that does not affect cyclosporine metabolism, may reduce gingival hyperplasia. Gingivectomy may occasionally be indicated, and switching from cyclosporine to tacrolimus is usually effective. Cosmetic complications tend to become less prominent with time. Sympathetic cosmetic

counseling is required. Cyclosporine may increase prolactin levels, occasionally producing gynecomastia in men and breast enlargement in women.

Hyperlipidemia. Cyclosporine has been implicated as one of the various factors responsible for the generation of post-transplantation hypercholesterolemia (see Chapter 10). The mechanism of this effect may be related to abnormal low-density lipoprotein feedback control by the liver, to altered bile acid synthesis, or to occupation of the low density lipoprotein receptor by cyclosporine. Up to two thirds of patients develop *de novo* hyperlipidemia in the first posttransplantation year. The effect is less marked with tacrolimus, and lipid levels may decrease when patients are switched from cyclosporine to tacrolimus.

Glucose Intolerance. Post-transplantation glucose intolerance and new-onset diabetes mellitus (NODM) are discussed in Chapter 10. Both calcineurin inhibitors

---

are toxic to pancreatic islets, although tacrolimus is more so, possibly as a result of increased concentrations in islets of FKBP relative to cyclophilin. The effect is dose related and may be exaggerated by concomitant corticosteroid use. Morphologic changes in the islets include cytoplasmic swelling, vacuolization, and apoptosis, with abnormal immunostaining for insulin. Obesity, African American or Hispanic ethnicity, family history of diabetes, and hepatitis C infection may predispose to NODM. Figure 5.3 shows the incidence of diabetes before and after transplantation by type of calcineurin inhibitor as reported to the United States Renal Data System.

Neurotoxicity. A spectrum of neurologic complications has been observed in patients receiving calcineurin inhibitors; they are generally more marked with tacrolimus. Coarse *tremor*, dysesthesias, headache, and insomnia are common and may be dose and blood-level related. Patients may complain of discrete cognitive difficulties coinciding with peak drug levels. More severe complications are uncommon in kidney recipients, although isolated seizures may occasionally occur, and full-blown leukoencephalopathy has been described. *Bone pain* in long bones has also been described.

Infection and Malignancy. Infection and malignancy inevitably accompany immunosuppression and are discussed in detail in Chapters 10 and 11. Despite their immunosuppressive potency, the incidence of infections and common *de novo* neoplasms has not significantly increased since the introduction of the calcineurin inhibitors, although the course of malignancies may be accelerated.

Thromboembolism. *In vitro,* cyclosporine increases adenosine diphosphate-induced platelet aggregation, thromboplastin generation, and factor VII activity. It also reduces production of endothelial prostacyclin. These findings may be causally related to the somewhat increased incidence of thromboembolic events

---

that have been observed in cyclosporine-treated kidney transplant recipients. The finding of glomerular microthrombi as part of calcineurin inhibitor-induced microangiopathy was discussed previously.

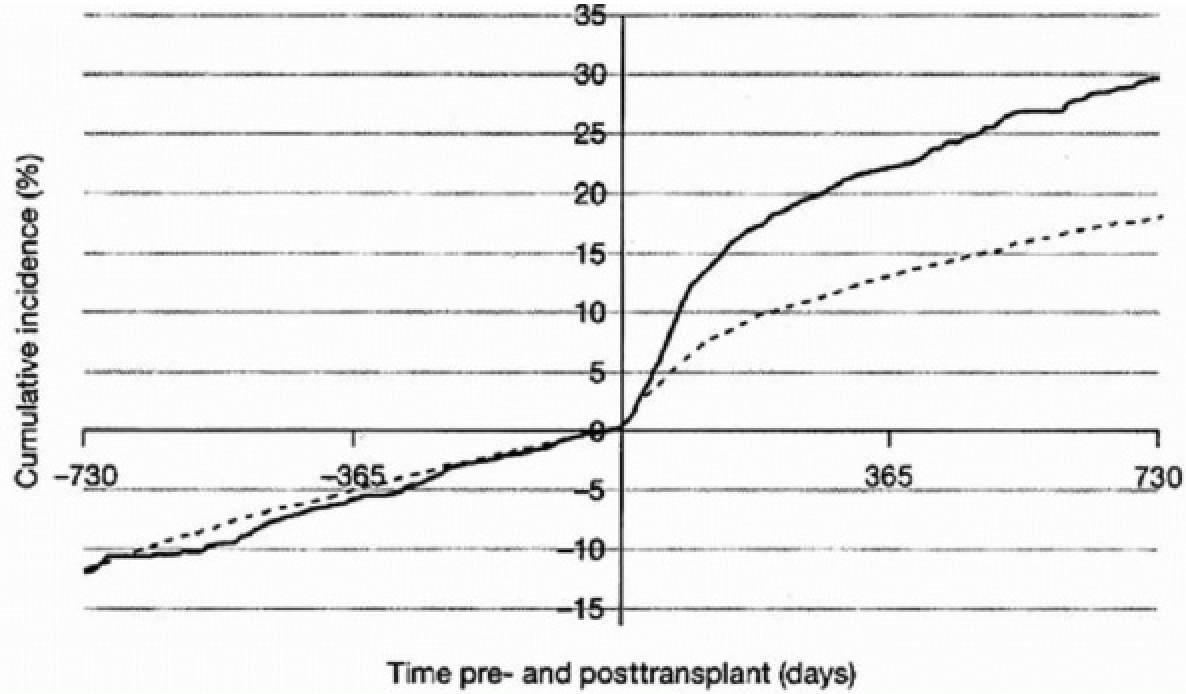


FIGURE 5.3 Incidence of diabetes before and after transplantation by type of calcineurin inhibitor *(solid line*, tacrolimus; *dashed line*, cyclosporine). Note that the incremental incidence of diabetes for cyclosporine was 9.4% at 1 year and 8.4% at 2 years. The incremental incidence of diabetes for tacrolimus use was 15.4% at 1 year and 17.7% at 2 years. (From Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. Am J Transplant 2003;3:590-598, with permission.)

Hyperuricemia and Gout. Hyperuricemia, because of reduced renal uric acid clearance, is a common complication of calcineurin inhibitor therapy, particularly when diuretics are also employed. Episodes of gout are more common in patients receiving cyclosporine than tacrolimus and have been reported in up to 7% of patients. Treatment is discussed in Chapter 10.

Mycophenolate Mofetil and Mycophenolic Acid

MMF (CellCept) was introduced into clinical transplantation in 1995 after a series of clinical trials (see Part III) showed that it was more effective than aza-thioprine for the prevention of acute rejection in recipients of cadaveric kidney transplants when used in combination with cyclosporine and prednisone. MMF is a prodrug, the active compound of which is mycophenolic acid (MPA), a fermentation product of several *Penicillium* species; the mofetil moiety serves to markedly improve its oral bioavailability. An enteric-coated form of MPA (ERL-080, Myfortic) became available in 2004. The role of MMF and MPA in clinical transplantation is discussed in Parts IV and V.

Generic formulations of MPA derivatives are available in some parts of the world and became available in the United States in 2009. It is unlikely that the generic formulations will undergo the same risk-benefit evaluation of the brand name drugs. Because therapeutic drug monitoring is not routinely performed during administration of these drugs, it will be difficult to determine their relative clinical effectiveness, and they should be used with caution.

Mechanism of Action

MPA is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is a critical, rate-limiting enzyme in the so-called *de novo* synthesis of purines and catalyzes the formation of guanosine nucleotides from inosine. Depletion of guanosine nucleotides by MPA has relatively selective antiproliferative effects on lymphocytes; lymphocytes appear to rely on *de novo* purine synthesis more than other cell types that have a "salvage" pathway for production of guanosine nucleotides from guanine (Plate 5.1 and Fig. 5.4). In principle, MPA is a more selective antimetabolite. It differs radically in its mode of action from the calcineurin inhibitors and sirolimus in that it does not affect cytokine production or the more proximal events following antigen recognition. It differs from azathioprine by virtue of its selective effect on lymphocytes. *In vitro*, MPA blocks the proliferation of T and B cells, inhibits antibody formation, and inhibits the generation of cytotoxic T cells. MPA also down-regulates the expression of adhesion molecules on lymphocytes, thereby impairing their binding to vascular endothelial cells. The capacity of MMF to treat ongoing rejection (see Part IV) may be a reflection of its ability to inhibit the recruitment of mononuclear cells into rejection sites and the subsequent interaction of these cells with target cells. MMF may also exert a preventive effect on the development and progression of proliferative arteriolopathy, a critical pathologic lesion in chronic rejection (see Chapter 14). Retrospective analyses suggest that MMF reduces the rate of late allograft loss by an effect that is both dependent and independent of its effect on the incidence of acute rejection.

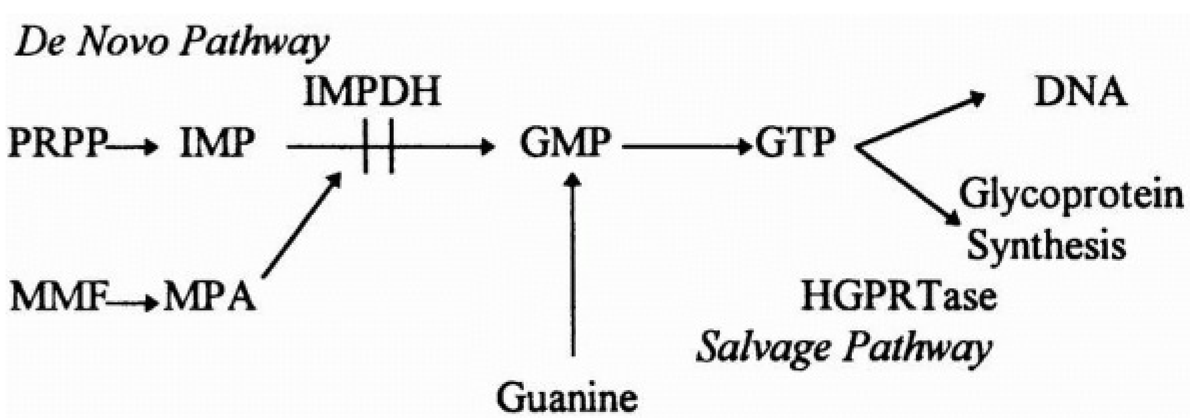


FIGURE 5.4 Mechanism of action of mycophenolate mofetil by inhibition of *de novo* purine synthesis. GMP, guanosine monophosphate; GTP, guanosine triphosphate; HGPRTase, hypoxanthine guanine phosphoribosyl transferase; IMP, inosine monophosphate; IMPDH, inosine monophosphate dehydrogenase; MPA, mycophenolic acid; PRPP, 5-phosphoribosyl-1-phosphate.

Pharmacology and Toxicity

Both MMF (CellCept) and enteric-coated MPA (Myfortic) are generally well tolerated and “user-friendly” compounds. CellCept is available for clinical use in 250-mg and 500-mg capsules: the standard dose is 1 g twice daily; Myfortic is available in 180-mg and 360-mg capsules: the standard dose when used is 720 mg twice daily. For African American patients, a higher dose may be required to produce the immunosuppressive benefit. An intravenous preparation is available but is usually not required in kidney transplant recipients.

The pharmacokinetics of MMF are complex. Orally administered MMF is rapidly absorbed and hydrolyzed to MPA in the liver, producing a peak level in 1 to 2 hours. MPA is then glucuronidated to an inactive form (MPAG). Entero-hepatic cycling of MPAG can occur producing a second peak that occurs at 5 to 6 hours, which may account for some of its GI side effects. Bioavailability of MMF in the capsule form is 90%, with a half-life of 12 hours. The AUC of MPA is increased by renal impairment, although dose adjustments are not usually made. Neither MMF nor MPA is dialyzed.

Extensive safety data are available from the clinical trials of MMF. The most common adverse events are related to the GI tract, with diarrhea occurring in up to one third of patients, and varying degrees of nausea, bloating, dyspepsia, and vomiting occurring in up to 20% of patients. Frank esophagitis and gastritis with occasional GI hemorrhage occur in about 5% of patients and may be associated with cytomegalovirus (CMV) infection. The incidence of GI side effects may be higher if the dosage is greater than 1 g twice daily. Most of these symptoms respond promptly to transient reduction of drug dosage. The total daily dose can also be split into three or four doses. The GI side affect profile of the enteric-coated formulation of MPA is not statistically significantly different from the original formulation.

Despite the relatively specific action of MPA on lymphocytes, leukopenia, anemia, and thrombocytopenia occur with a frequency similar to that seen with azathioprine and may require dose adjustment. Prolonged leukocytosis may also occur. The incidence of lymphoproliferative disorders and opportunistic infections in all the various clinical trials of MMF is marginally greater than that seen in control groups and is a nonspecific reflection of its greater immunosuppressive potency. Rare cases of progressive multifocal leukoencephalopathy (PML) have been described in patients receiving MMF, although it is difficult to definitively ascribe this catastrophic complication to the drug.

Nephrotoxicity, neurotoxicity, and hepatotoxicity have not been observed with MMF.

Congenital malformations including ear malformations have been reported in offspring of patients exposed to MMF during pregnancy, and MPA derivatives are regarded as being unsafe for use in pregnancy. The drugs should be

discontinued before planned pregnancy in both males and females; immunosuppressive drug protocol adjustments may be required.

Several studies have described a relationship between the AUC for MPA and its clinical efficacy and side-effect profile. The relationship to random trough levels is less consistent. Therapeutic drug monitoring is generally not required for routine clinical management. In the event of side effects, the longer the period of drug-dose reduction or discontinuation, the greater is the subsequent incidence of episodes of acute rejection. Hence, the drug should be reintroduced as soon as possible and the clinical course carefully monitored.

Drug Interactions

MPA is not metabolized through the CYP3A enzyme system, and the multiple drug interactions seen with the calcineurin inhibitors do not occur. MMF and azathioprine should not be administered concomitantly because of the potential for combined hematologic toxicity. Standard hematologic parameters must be carefully followed when MMF is used with sirolimus (see Part IV). Cyclosporine lowers MPA concentrations by decreasing its enterohepatic recycling. Trough levels of MPA increase when cyclosporine administration is discontinued. This interaction is not seen with tacrolimus or sirolimus, and the maintenance dosage of MMF, when used with standard doses and blood levels of these two drugs, is typically 500 mg to 750 mg twice daily. MMF should not be administered simultaneously with antacids, cholestyramine, sevelamer, or oral ferrous sulfate, all of which decrease intestinal absorption. MMF, as opposed to azathioprine, can be administered with allopurinol without dose adjustment. Potential interaction may occur when MMF is administered concomitantly with acyclovir and ganciclovir, and it is wise to discontinue MMF when there is evidence of systemic herpes infection necessitating use of these drugs.

mTOR Inhibitors: Sirolimus and Everolimus

The mTOR (mammalian target of rapamycin) is a key regulatory kinase in the process of cell division. The term *TOR* or *mTOR inhibitor* refers to two similar immunosuppressant drugs whose mode of action (see “Mechanism of Action,” below) is closely linked to inhibition of this kinase. Sirolimus (Rapamune), also known as *rapamycin,* is a macrolide antibiotic compound that is structurally related to tacrolimus. Everolimus (Certican), also known as *RAD,* is a similar compound with a shorter half-life. Most of the clinical experience with this class of immunosuppressants is with sirolimus, which is the only TOR inhibitor available for clinical use in the United States.

Sirolimus was introduced into clinical transplantation in the United States in 1999, after a series of clinical trials (see Part III) demonstrated that, when used in combination with cyclosporine and prednisone, it produced a significant reduction in the incidence of acute rejection episodes in the early posttransplantation period, compared with either azathioprine or placebo. These trials were similar in design to those that led to the introduction of MMF in that full doses of cyclosporine were administered and therapeutic drug monitoring was not routinely performed. In Europe, its introduction was delayed because of concerns regarding impairment of kidney function documented in similar trials. It was eventually approved for use in Europe in a protocol based on withdrawal of cyclosporine starting 3 months after transplantation (see "Side Effects"). Sirolimus has also been used with tacrolimus, with prednisone without a calcineurin inhibitor, and with or without MMF. Sirolimus has not been rigorously compared with MMF; it is probably a more potent but also a more toxic immunosuppressant. The place of sirolimus in clinical transplantation and dosing recommendations are discussed in Part IV.

Mechanism of Action

The immunosuppressive activity of the mTOR inhibitors appears to be mediated through a mechanism distinct from that of the calcineurin inhibitors. Like the calcineurin inhibitors, they bind to a cytoplasm-binding protein (the same one that binds tacrolimus, FKBP). The resultant sirolimus-FKBP ligand, however, does not block calcineurin (see Chapter 2, Plate 5.1, and "Mechanism of Action" under "Calcineurin Inhibitors," above); instead, it engages a protein designated *target of rapamycin* because its discovery was related to studies on the mechanism of action of rapamycin. TOR is a key regulatory kinase, and its inhibition reduces cytokine-dependent cellular proliferation at the G_1 to S phase of the cell-division cycle. Both hematopoietic and nonhematopoietic cells are affected. Because rapamycin occupies the same binding protein as tacrolimus, it was originally presumed that it would impair the action of tacrolimus; the drug was thus developed in clinical trials as an adjunctive agent with cyclosporine. It now appears that the abundance of FKBP *in vivo* makes it unlikely that there would be inhibitive competition of tacrolimus and sirolimus for their receptor, and the drugs are often used in combination.

Pharmacology

Sirolimus is available as a 1-mg or 2-mg capsule. It is rapidly absorbed from the GI tract, reaching peak concentrations in 1 to 2 hours. It has a long half-life, averaging 62 hours, and a steady-state trough concentration can be achieved in most patients within 24 hours by administering a loading dose 3 times the size of the maintenance dose. Everolimus has a half-life of 23 hours and is usually not administered with a loading dose. Both drugs are largely metabolized by the liver by both CYP3A and *p*-glycoprotein;

the native compound is the major component in human blood and contributes most of the immunosuppressive activity. Renal excretion is minimal, and dose adjustment is not required in renal dysfunction but is required in hepatic dysfunction. Therapeutic drug-level monitoring was not required in the initial labeling of sirolimus, but it has since become an essential component of its use. The target trough levels, using a HPLC assay, vary between 5 and 15 ng/dL, depending on the concomitant use of a calcineurin inhibitor and the clinical circumstances and are a good reflection of drug exposure. Because sirolimus has a long half-life, levels should be checked several days after a dosage adjustment is made, and once a steady state has been reached, frequent monitoring may not be required.

Drug Interactions

The TOR inhibitors and the calcineurin inhibitors are frequently administered together and are metabolized by the same enzyme systems; therefore, the potential for interaction between them must be considered. In healthy volunteers, concomitant administration of sirolimus and the Neoral formulation of cyclosporine increased the AUC for sirolimus by 230%, when compared with administration of sirolimus alone; administration 4 hours after the cyclosporine dose increased the AUC by 80%. For this reason, it has been recommended that sirolimus be administered consistently 4 hours after the morning cyclosporine dose. In clinical practice, however, this recommendation is often ignored, which might account for some of the toxicity noted below (see “Side Effects”). The effect of sirolimus on cyclosporine metabolism is less marked, but over time, lower doses of cyclosporine are required to maintain target trough levels. Sirolimus and tacrolimus are typically administered simultaneously. Available information suggests, not surprisingly, that sirolimus interacts with calcium channel blockers, antifungal agents, anticonvulsants, and antituberculous agents in a manner similar to the calcineurin inhibitors.

Side Effects

Nephrotoxicity. The TOR inhibitors, when administered alone, do not produce either the acute or chronic reductions in GFR that have been so consistently observed with calcineurin inhibitors. When administered with standard doses of calcineurin inhibitors, however, there appears to be a potentiation of nephrotoxicity that is not fully explained by their pharmacokinetic interaction. This phenomenon has been observed both in clinical trials and routine clinical use and is the basis for the recommendation that when the drugs are used in combination, the dose of the calcineurin inhibitor should be an attenuated one (see Part IV). When cyclosporine is withdrawn from the cyclosporine-sirolimus combination 3 months after transplantation, there is a consistent and persistent improvement in renal function. This is manifested not only in lower serum creatinine levels and higher GFR but also in lower uric acid levels and blood pressure and less marked chronic histologic damage. The TOR inhibitor may be

tubulotoxic and may produce hypokalemia and hypomagnesemia as a result of kaliuresis and magnesuria.

De novo proteinuria, nephrotic syndrome, and exaggeration of preexisting proteinuria have been observed with TOR inhibitor administration, possibly as a result of reduced tubular protein reabsorption and impaired podocyte integrity. Periodic quantitative monitoring of urinary protein excretion is recommended, and administration of TOR inhibitors in proteinuric patients should be avoided. TOR inhibitors have been associated with the development of localized limb edema and angioedema. Their concomitant use with other drugs known to cause angioedema, such as angiotensin-converting enzyme inhibitors, may increase the risk.

Impaired Healing. The TOR inhibitors block a critical step in cell division, and it is not surprising that their use would be associated with various manifestations of impaired healing and fibrogenesis. This property has been exploited in the coating of coronary artery stents with sirolimus to reduce the incidence of restenosis and may theoretically be of benefit in slowing tumor progression (see "Hematologic and Oncologic Effects," below). Sirolimus may delay recovery from post-transplantation delayed graft function by perpetuating acute tubular necrosis. The combination of sirolimus and tacrolimus has been reported to produce acute renal failure with a "cast nephropathy" as a consequence of tubular injury similar to that seen in myeloma. An increased incidence of lym-phoceles and dehisced, poorly granulating wounds may occur when TOR inhibitors are used in the early postoperative period, particularly in obese patients. Painful mouth ulcers may also occur that resolve when the drug is discontinued.

Effects on Reproductive Health. In animal models, sirolimus is embryotoxic and fetotoxic. Its use is contraindicated in pregnancy, and effective contraception must be initiated before, during, and for 12 weeks after therapy has been stopped. Reversible oligospermia and reduced testosterone levels have been described during sirolimus administration, and male patients should be informed accordingly.

Hyperlipidemia and Hyperglycemia. Hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia are common accompaniments of TOR inhibitor use and may occur in varying degrees in more than 50% of patients receiving these drugs. The effect has been ascribed to inhibition of lipoprotein lipase or to reduced catabolism of apoB100-containing lipoproteins. The hyperlipidemia is more pronounced for patients also receiving cyclosporine and tends to reach a peak 2 to 3 months after transplantation. In most patients, the elevation is

---

manageable with treatment with statins, and based on the Framingham risk model, the associated coronary heart disease (CHD) risk is small. In an animal model of aortic atherosclerosis, sirolimus was described as having a protective effect despite the hyperlipidemia, presumably because of an anti-inflammatory effect. The overall impact of TOR inhibitors on clinical CHD has not been defined, but for most patients, the degree of hyperlipidemia does not contrain-dicate their use. TOR inhibitors may also be

islet toxic and glucose metabolism does not improve when they are used in place of calcineurin inhibitors.

Pneumonia. In the early clinical trials of sirolimus, several cases of fatal *Pneumocystis* pneumonia were described in patients who did not receive prophylactic Bactrim. For this reason, it is recommended that Bactrim prophylaxis be continued for a least 1 year for patients receiving the drug (see Chapter 11). A noninfectious interstitial pneumonia has also been described, typically presenting as bilateral lower-lobe interstitial pneumonia. Pathologic features are similar to bronchiolitis obliterans organizing pneumonia with alveolar hemorrhage and lymphocytic infiltration. The diagnosis is one of exclusion, and the pneumonia typically resolves with 2 to 3 weeks of drug discontinuation.

Hematologic and Oncologic Effects. The TOR inhibitors can produce reversible "cytopenias," as do MMF and azathioprine, although the thrombocytopenia and anemia may be more pronounced. Hepatic artery thrombosis has been described in liver transplant recipients, but no increased thrombotic tendency has been described in kidney recipients. Thrombotic microangiopathy, well described with the calcineurin inhibitors (see "Acute Microvascular Disease" and Chapter 9), occurs with greater frequency when calcineurin inhibitors are used in combination with sirolimus, and cases have been described when it sirolimus is used alone.

In the clinical trials and clinical experience of the TOR inhibitors, the incidence of malignancy and post-transplantation lymphoproliferative disease has been small. In animal models, sirolimus inhibits primary and metastatic tumors through antiangiogenesis and arrests malignant cell growth in the G_1/S phase. The potential of unlinking immunosuppression from tumor progression is clearly of critical importance in transplantation. Conversion from cyclosporine to sirolimus has been shown to be effective treatment for cases of Kaposi sarcoma, and in the CONVERT trial (see Part IV), the incidence of malignancy was lower in patients who were converted from cyclosporine-based to sirolimus-based immunosuppression. The role of mTOR inhibitors in the management of post-transplant malignancy is discussed by Monaco in Selected Readings.

Azathioprine

Azathioprine (Imuran) is an antimetabolite, an imidazole derivative of 6-mercaptopurine. It has been used in clinical transplantation for nearly 40 years. When cyclosporine was introduced, the role of azathioprine was largely relegated to that of an adjunctive agent, and with the introduction of MMF, its use has been discontinued in many programs. It can still be a valuable component of a low-cost immunosuppressive regimen (see Part IV).

Mode of Action

Azathioprine is a purine analogue that is incorporated into cellular deoxyribonucleic acid (DNA), where it inhibits purine nucleotide synthesis and interferes with the synthesis and metabolism of ribonucleic acid (RNA) (Plate 5.1). Unlike cyclosporine, it does not prevent gene activation, but it inhibits gene replication and consequent T-cell activation. Azathioprine is a broad myelocyte suppressant. It inhibits the proliferation of promyelocytes in the bone marrow and, as

---

a result, it decreases the number of circulatory monocytes capable of differentiating into macrophages. Thus, it is a powerful inhibitor of the primary immune response and is valuable in preventing the onset of acute rejection. It is ineffective in the therapy of rejection episodes.

Side Effects

The most important side effects of azathioprine are hematologic. Complete blood counts, including a platelet count, should be performed weekly during the first month of therapy, and less frequently thereafter. Delayed hematologic suppression may occur. In the event of significant thrombocytopenia or leukopenia, the drug can be discontinued for long periods if the patient is also taking a calcineurin inhibitor, without great danger of inducing acute rejection. It is unnecessary to maintain a low white blood cell count for the drug to be an effective immunosuppressant.

The white blood cell count should be monitored with particular care when the corticosteroid dose is reduced or discontinued. Azathioprine may occasionally cause hepatitis and cholestasis, which usually present as reversible elevations in transaminase and bilirubin levels. The azathioprine dose is usually reduced or stopped during episodes of significant hepatic dysfunction. Pancreatitis is a rare complication. Azathioprine is converted to inactive 6-thiouric acid by xanthine oxidase. The inhibition of this enzyme by allopurinol demands that this drug combination be avoided or used with great care. When allopurinol is started, the azathioprine dose should be reduced to 25% to 50% of its initial level, and the white blood cell and platelet counts should be frequently monitored.

Dose and Administration

About half of orally administered azathioprine is absorbed; thus, the intravenous dose is equivalent to half the oral dose. Blood levels are not valuable clinically because its effectiveness is not blood-level dependent. The drug is not significantly dialyzed or excreted by the kidney. Dose reduction is often practiced during kidney dysfunction, although it may not be necessary. When used as the primary immunosuppressant, the daily oral dose is 2 to 3 mg/kg. When used as adjunctive therapy with a calcineurin inhibitor, the dose is 1 to 2 mg/kg.

Corticosteroids

Corticosteroids have commanded a central position in clinical transplantation since they were first used to treat rejection in the 1960s. Despite this long experience, there remains only a general consensus on their best therapeutic use, and changing protocols often reflect both fear of prescribing them and fear of not prescribing them. The new generation of immunosuppressive drugs and protocols permit avoidance or withdrawal of corticosteroids for many patients, and in patients who continue to receive them, the dosage is typically quite small (see Part IV).

The diffuse effects of corticosteroids on the body reflect the fact that most mammalian tissues have glucocorticoid receptors within the cell cytoplasm and can serve as targets for the effects of corticosteroids. The immunosuppressive actions of corticosteroids can be somewhat simplistically divided into their specific actions on macrophages and T cells and their broad, nonspecific immunosuppressant and anti-inflammatory actions.

Mechanism of Action

Blockade of Cytokine Gene Expression. Corticosteroids exert their most critical immunosuppressive effect by blocking T-cell-derived and APC-derived cytokine and cytokine receptor expression. They inhibit the function of dendritic cells, which are the most important of the APCs (see Chapter 2). They are hydrophobic and can diffuse intracellularly, where they bind to cytoplasmic receptors found in association with the 90-kDa heat shock protein. As a result, the heat shock protein becomes dissociated, and the steroid-receptor complex translocates to the nucleus, where it binds to DNA sequences referred to as *glucocorticoid response elements* (GREs). GRE sequences have been found in the critical promoter regions of several cytokine genes, and it is presumed that the binding of the steroid-receptor complex to the GRE inhibits the transcription of cytokine genes. Corticosteroids also inhibit the translocation to the nucleus of nuclear factor-κB, a transcription factor that plays a major role in the induction of genes encoding a wide variety of cytokines. Corticosteroids inhibit the expression of IL-1, IL-2, IL-3, and IL-6, TNF-α, and IFN-γ. As a result, all stages of the T-cell activation process are inhibited. Cytokine release is responsible for the fever often associated with acute rejection. This fever typically resolves rapidly when high-dose corticosteroids are administered.

Nonspecific Immunosuppressive Effects. Glucocorticoids cause a lymphopenia that is a result of the redistribution of lymphocytes from the vascular compartment back to lymphoid tissue. The migration of monocytes to sites of inflammation is also inhibited. Steroids block the synthesis, release, and action of a series of chemokines, permeability-increasing agents, and vasodilators, although these anti-inflammatory effects are a relatively minor aspect of their efficacy in the prevention and treatment of acute rejection. The total white blood cell count may rise several-fold during high-dose steroid administration.

Complications

The ubiquitous complications of corticosteroids are familiar to medical practitioners and are not reviewed here in detail. They are a reflection of their profound immunosuppressive, anti-inflammatory, and hormonal action on numerous target tissues. The most important complications are cosmetic changes, growth impairment, osteonecrosis, osteoporosis, impaired wound healing and resistance to infection, cataracts, hyperlipidemia, glucose intolerance, and psychopathologic effects. There is marked variation in individual response to these drugs, presumably because of the varied concentration of tissue steroid receptors and individual variations in prednisone metabolism. In the dose regimens currently prescribed, untoward complications can be minimized, but not totally prevented.

Commonly Used Preparations

In clinical transplantation, steroids are used in three ways: as a high-dose intravenous or oral pulse given over 3 to 5 days; as a steroid cycle or taper with a gradually decreasing oral dose over days or weeks; or as a steady low-dose daily or every-other-day maintenance regimen. Corticosteroid dosage is discussed in Part IV.

Prednisolone, its 11-keto metabolite *prednisone,* and *methylprednisolone* (Solu-Medrol) are the corticosteroid preparations most commonly used in clinical transplantation. Prednisolone is the most active circulating immunosuppressive corticosteroid. Prednisone is the oral preparation usually used in the United States, whereas prednisolone is often preferred in Europe. Methylprednisolone is the most commonly used intravenous corticosteroid. These preparations have a half-life that is measured in hours, but their capacity to inhibit lymphokine production persists for 24 hours; therefore, once-daily administration is adequate.

Corticosteroids are metabolized by hepatic microsomal enzyme systems. Drugs such as phenytoin, barbiturates, and rifampin, which induce these enzymes, may lower plasma prednisolone levels, whereas oral contraceptives and ketoconazole increase levels. Unfortunately, there is no readily available plasma prednisolone assay for clinical use, although empirical adjustments in dose may be advisable when potentially interacting drugs are administered.

PART II. BIOLOGIC IMMUNOSUPPRESSIVE AGENTS

MONOCLONAL AND POLYCLONAL ANTIBODIES

The antilymphocyte polyclonal antibodies are produced by immunizing either horses or rabbits with human lymphoid tissue and then harvesting the resultant immune sera to obtain gammaglobulin fractions. Various polyclonal antibodies have been available for

use in clinical transplantation since the 1970s. Currently, the only polyclonal antibodies widely available for clinical use are preparations of Thymoglobulin. The intravenous immune globulins (IVIGs), which have been used in the treatment of antibody deficiency disorders for more than 30 years, are finding increasing relevance to current transplant therapeutics. They are made from pooled human plasma.

The monoclonal antibody muromonab-CD3 (Orthoclone OKT3, referred to here simply as *OKT3*) has been available for clinical use since 1987, although its use has been largely superseded by Thymoglobulin. The humanized anti-Tac (HAT) monoclonal antibody preparations daclizumab and basiliximab became available in 1998. Rituximab is an anti-B-cell monoclonal antibody developed for the treatment of hematologic malignancies that has proved useful in clinical transplantation. Alemtuzumab (Campath 1H) is an anti-CD52 humanized monoclonal antibody approved for use in B-cell chronic lymphocytic leukemia and now used in transplantation. Belatacept (CTLA4Ig) is in advanced stages of clinical development and is discussed together with other new monoclonal antibodies in various stages of development in Part III.

Biologic immunosuppressive agents can be used for induction immunosuppression and for the treatment of acute rejection; they are not currently used for maintenance immunosuppression. Table 5.3 reviews their major indications, which are discussed in detail in Part IV. The polyclonal antibodies (IVIG excluded), OKT3, and alemtuzumab cause varying degrees of T-cell depletion and are sometimes referred to as *depleting antibodies;* the HAT

---

monoclonal antibodies and belatacept cause T-cell dysfunction but are "nondepleting."

TABLE 5.3 Antibody Preparations for Renal Transplant Immunosuppression

	Indication		**Mechanism of Action**
Treatment	**Induction**	**Rejection**	**Lymphocyte Depletion**
Monoclonal			

OKT3	(+)	+	Yes
Basiliximab	+*	—	No
Daclizumab	+*	—	No
Polyclonal			
Atgam	+	+	Yes
Thymoglobulin	(+)	+	Yes

+, Approved indication; (+) unapproved but commonly used indication;

* , concomitant administration of calcineurin inhibitor recommended.

Thymoglobulin

Thymoglobulin is a polyclonal antibody preparation made by immunization of rabbits with human lymphoid tissue, it has largely replaced Atgam, which is made by the immunization of horses with human lymphoid material and is less potent. In the case of Thymoglobulin (Genzyme), which is available in the United States, thymocytes are used

for immunization; in the case of anti-T-lymphocyte immune globulin (ATG-Fresenius), which is available in Europe, an activated human T-cell line is used. The resultant gammaglobulin is then purified to remove irrelevant antibody material that may be responsible for some of the side effects.

Mode of Action

The precise mechanism of action of the polyclonal antibodies is not fully understood, but the immunosuppressive product contains cytotoxic antibodies directed against a variety of T-cell markers. After their administration, there is depletion of peripheral blood lymphocytes. The lymphocytes, T cells in particular, are either lysed or cleared by the reticuloendothelial system, and their surface antigens may be masked by the antibody. Of particular importance, Thymoglobulin causes sustained and rapid expansion of $CD4^+$, $CD25^+$, $FOXP3^+$ regulatory T cells that play an important part in maintaining immune homeostasis and limiting antigraft immunity (see Chapter 2). High levels of these cells improve the probability of reversal of acute rejection and lower the risk for graft loss after a rejection episode. Following the use of Thymoglobulin, a prolonged lymphopenia can ensue, and the CD4 subset may be suppressed for several years. The prolonged immunosuppressive effect may account for the relative infrequency of episodes of rejection recurrence.

Dose and Administration

The standard dose of Thymoglobulin is 1.5 mg/kg given in a course lasting 4 to 10 days. When Thymoglobulin is used for induction, it may be more effective when started intraoperatively (rather than postoperatively) in reducing the incidence of delayed graft function. Thymoglobulin may also be effectively dosed based on its impact on T-cell subsets. It is mixed in 500 mL of dextrose or saline and infused over 4 to 8 hours into a central vein or arteriovenous fistula. Use of a peripheral vein is sometimes followed by vein thrombosis or thrombophlebitis, although this may be prevented by adding hydrocortisone sodium succinate (Solu-Cortef), 20 mg, and heparin, 1,000U, to the infusion solution. To avoid allergic reactions, the patient should receive intravenous premedication consisting of methylprednisolone, 30 mg, and diphenhydramine hydrochloride (Benadryl), 50 mg, 30 minutes before injection. Acetaminophen should be given before and 4 hours after commencement of the infusion for fever control. Vital signs should be monitored every 15 minutes during the first hour of infusion and then hourly until the infusion is complete.

Azathioprine, MMF, and sirolimus should generally be discontinued during the course of treatment to avoid exacerbating hematologic side effects. Cyclosporine or tacrolimus can be omitted during the course or given in a low dose, and oral prednisone is replaced by the methylprednisolone given in the premedication.

Side Effects

Most of the side effects of polyclonal antibodies relate to the fact that foreign protein is administered. Chills, fever, and arthralgias are common, although the severe first-dose reactions seen with OKT3 occur only rarely. There have been

occasional cases of anaphylaxis. Serum sickness occurs rarely because the continued immunosuppression that follows the treatment course reduces the production of anti-idiotypic antibodies and the consequent immune complex deposition. Serum sickness typically presents with diffuse arthralgias, fever, malaise, and rash. It responds to an increase in prednisone dose to about 40 mg daily for several days.

Polyclonal antibody preparations can produce thrombocytopenia and leukopenia, necessitating reduction or curtailment of drug dosage. Leukopenia occurs in up to half of patients. The drug dose is usually halved for patients with either a platelet count of 50,000 to 100,000 cells/mL or a white blood cell count of less than 3000 cells/mL. Administration should be stopped if the counts fall further.

Infection, most commonly with CMV, may be a late adverse sequela of depleting antibody use. The frequency of infection varies with the number of courses and the overall amount of immunosuppression given. Most programs routinely employ CMV prophylaxis before or during a course of depleting antibody, with recipients of CMV-positive allografts representing a particularly high-risk population.

The development of lymphoma in transplant recipients is a well-recognized, although infrequent, consequence of effective immunosuppression. Use of repeat courses of depleting antibodies is associated with a particularly fulminant and typically rapidly fatal B-cell lymphoma that develops within the first few months after transplantation. Epstein-Barr virus (EBV) antibody-negative patients receiving a graft from an EBV-positive donor appear to be at greatest risk. The recognition, prevention, and management of posttransplant lymphoma are discussed in Chapters 10 and 11.

OKT3

OKT3 is lymphocyte-depleting monoclonal antibody that was used widely in clinical transplantation but has fallen into disfavor largely because of its potentially life-threatening first-dose reaction and the introduction of the similarly effective but less toxic Thymoglobulin. As of 2009, many transplantation program pharmacies in the United States have stopped stocking OKT3, and the drug has to be ordered on an individual patient basis. It is now used when Thymoglobulin is contraindicated, usually because of leukopenia or thrombocytopenia.

Mode of Action

OKT3 is an immunoglobulin G (IgG) globulin—a monoclonal antibody produced by the hybridization of murine antibody-secreting B lymphocytes with a nonsecreting myeloma cell line whose neoplastic potential permits the secretion of antibody in perpetuity.

Compared with the humanized monoclonal antibodies, OKT3 is *xenogeneic* because the whole antibody is of murine origin. OKT3 reacts with human T cells by binding to one of the 20-kDa subunits of the CD3 complex, an intrinsic part of the T-cell receptor (see Chapter 2 and Plate 5.1). The subsequent deactivation of the CD3 complex causes the T-cell receptor to undergo endocytosis and to be lost from the cell surface. The T cells become ineffectual, and within 1 hour, they become opsonized and are removed from the circulation into the reticuloendothelial system. OKT3 also blocks the function of killer T cells.

Concomitant with the initial depletion of $CD3^+$ cells, there is depletion of T cells with other surface markers (CD4, CD8, CD11). Within a few days, T cells reappear in the circulation that carry CD4, CD8, and CD11 markers but are devoid of CD3 and are hence ineffectual, or *modulated*, cells. $CD3^+$ functional

---

cells may reappear later in the course of OKT3 because of the production of neutralizing antibodies.

Dose and Administration

The standard dose of OKT3 is 5 mg given as an intravenous bolus through a Millipore filter. The standard course consists of a daily dose for 10 days, although shorter courses are sometimes given. Readers are referred to the package insert for precise OKT3 protocol recommendations. The first few doses of OKT3 must be given in the hospital, preferably at an institution familiar with its use, side effects, and clinical indications. If the drug is well tolerated, the course can be completed on an outpatient basis with substantial financial economy and patient convenience.

Side Effects

The infection and lymphoma risks of OKT3 administration are similar to those described for Thymoglobulin. Significant, potentially life-threatening adverse reactions may occur during the first days of treatment with OKT3. These adverse reactions occur as the percentage of potent T cells plummets and a series of T-cell-derived cytokines are released into the circulation. The term *cytokine release syndrome* has been used to describe the clinical events that follow.

After the first exposure to OKT3, nearly all patients become febrile, and many suffer rigors. The fever and rigors often occur “like clockwork” 45 minutes after the injection but may be delayed for hours. By the second or third dose, the fever typically abates, although some patients remain febrile for several days or throughout the whole course. If the fever is prolonged for more than two or three doses, a fever workup should be performed. Transient graft dysfunction with elevated creatinine levels may occur as part of the cytokine release syndrome.

A rapidly developing, potentially life-threatening noncardiogenic pulmonary edema

may occur after the first or second dose of OKT3 if the patient is over their "dry weight" at the time of injection. Even euvolemic patients may wheeze and become dyspneic. Post-OKT3 pulmonary edema is a largely preventable syndrome as long as the patient is euvolemic at the time of drug administration. Clinical volume assessment is often unreliable, and patients may "hide" liters of fluid that are not clinically detectable. It is often wise and expeditious to dialyze or ultrafilter a patient before OKT3 administration to ensure that the required amount of fluid is removed. After the first doses of OKT3, the fluid restrictions can be relaxed.

A spectrum of neurologic complications can occur during a course of OKT3, varying in severity from a commonly occurring mild headache to severe encephalopathy. The aseptic meningitis syndrome is self-limited and typically resolves spontaneously without the necessity for discontinuing the OKT3 course. If a lumbar puncture is performed, a mild culture-negative leukocytosis with pleocytosis is often found. About one third of patients with a diagnosis of aseptic meningitis have coexisting evidence of encephalopathy. OKT3 should be discontinued in severely encephalopathic patients.

Episodes of rejection may occur after up to 60% of courses of OKT3. These episodes, which are typically mild, can usually be controlled with a low-dose prednisone pulse. They occur as potent $CD3^{+}$ T cells reappear in the circulation. At the completion of a course of OKT3, it is important to ensure that calcineurin inhibitor blood levels are in the high therapeutic range.

Alemtuzumab

Alemtuzumab (Campath 1H) is a recombinant DNA-derived humanized monoclonal antibody directed against the cell surface glycoprotein CD52 (Plate 5.1)

---

approved for use in chronic lymphocytic leukemia that is a potentially valuable depletional agent in clinical transplantation, although it has not been formally approved for such use. It has also been used in the treatment of acute transplant rejection. When used at the time of transplantation as induction therapy (see Part IV), alemtuzumab induces a profound, rapid, and effective depletion of peripheral and central lymphoid cells that may take months to return to pretransplantation levels. Used as a single agent, it does not induce tolerance and episodes of acute rejection can occur even in the absence of T cells. Its use may facilitate minimization of maintenance immunosuppressive protocols and steroid sparing with monotherapy using sirolimus or low-dose calcineurin inhibitor. The terms *prope tolerance* and *near tolerance* have been used to describe the immunologic balance that results.

Alemtuzumab use in kidney transplantation is "off-label." Its ease of administration and relatively low cost have made it an attractive alternative to Thymoglobulin. Alemtuzumab, however, has not undergone the kind of clinical trials and rigorous evaluation required to achieve a formal indication. Neither has it undergone extensive comparison with Thymoglobulin, with which it competes. It is usually given as a single

dose of 30 mg intraoperatively, a second dose is sometimes given. Because the drug is administered under general anesthesia, infusion-related events typically associated with the infusion of biologic agents are masked.

Alemtuzumab induces profound lymphopenia, which may be prolonged requiring reduced doses of other myelosuppressive agents. There may be delayed incidence of cell-mediated acute rejection and possibly a higher incidence of antibody-mediated rejection that occurs as lymphocyte counts return to baseline. The hematologic, infection, and lymphoma risks are similar to those described for other depletional agents, and infection prophylaxis is mandatory.

Intravenous Immune Globulins

Pooled human gammaglobulin preparations, which were initially developed for the treatment of humoral immune deficiency disorders, are now used for a variety of autoimmune and inflammatory disorders. They are proving to be invaluable in certain defined situations in clinical transplantation when used alone or in combination with plasmapheresis (Table 5.4). Immune globulin preparations are made from pooled plasma from thousands of blood donors in a tightly regulated manufacturing process that essentially removes the risk for transmission of infectious disease. Immune globulins may be unselected, in which case they contain IgG molecules with a subclass distribution corresponding to that in normal human serum; they may also be selected because of the high titer of desired antibody in the donor plasma. CMV hyperimmune globulin (CMVIG, marketed in the United States as CytoGam), approved for CMV prophylaxis and treatment (see Chapter 11), is made from blood donors with a high titer of anti- CMV antibody.

TABLE 5.4 Clinical Uses of Immune Globulin Preparations in Transplantation

1.	To reduce high levels of preformed anti-HLA antibodies in sensitized patients awaiting deceased donor transplants (see Chapters 3 and 7).
2.	To facilitate living donor transplants in the face of a positive crossmatch or ABO incompatibility (see Chapters 3, 6, and 7).

3.	To treat acute humoral rejection (see Part IV and Chapter 9).
4.	To treat certain post-transplantation viral infection (see Chapter 11).

Mechanism of Action

The mode of action of IVIG is complex (Table 5.5), and the broad range of its activities is a reflection of the importance of immunoglobulins in immune homeostasis in health. In highly sensitized patients, IVIG inhibits anti-HLA antibody and produces long-term suppression or elimination of anti-HLA reactive T cells and B cells. The cytokine signaling, critical for IgG synthesis, is inhibited, and alloimmunization is inhibited through blockade of the T-cell receptor (see Chapter 2). Although discussed here in the context of immunosuppressant medications, IVIG is better regarded as immunomodulatory in its activity, and its use is not associated with the familiar complications of immunosuppression.

Dosage, Administration, and Side Effects

The dose of IVIG is protocol dependent, and readers should consult the package insert and administration precautions of individual preparations before their use. All preparations are administered slowly over several hours. The standard dose of is 2 g/kg up to a maximum of 140 g in a single administration given over 4 to 8 hours. The dose of CMVIG varies from 100 to 150 mg/kg and is often given following plasmapheresis, with one plasma volume exchange replaced by either 5% albumin or fresh-frozen plasma. Minor reactions, such as flushing, chills, headache, nausea, myalgia, and arthralgia, occur in about 5% of patients soon after commencement of IVIG infusions. These symptoms resolve when the infusion is temporarily discontinued or its rate reduced. Aseptic meningitis, which can be prevented by the administration of nonsteroidal anti-inflammatory agents, may occur in the first 72 hours following the infusion; it typically resolves spontaneously.

TABLE 5.5 Immunoregulatory Effects of Immune Globulin

Fc Receptors

Blockade of Fc receptors on macrophages and effector cells

Induction of antibody-dependent cellular cytotoxicity

Induction of inhibitory Fcγ receptor IIB

Inflammation

Attenuation of complement-mediated damage

Decrease in immune complex-mediated inflammation

Induction of anti-inflammatory cytokines

Inhibition of activation of endothelial cells

Neutralization of microbial toxins

Reduction in corticosteroid requirements

B Cells and Antibodies

Control of emergent bone marrow B-cell repertoires

Negative signaling through the Fcγ receptors

Selective down-regulation and up-regulation of antibody production

Neutralization of circulating autoantibodies by anti-idiotypes

T Cells

Regulation of the production of helper T-cell cytokines

Neutralization of T-cell superantigens

Cell Growth

Inhibition of lymphocyte proliferation

Regulation of apoptosis

From Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. N Engl J Med 2001;345:747-755, with permission.

Thrombotic complications have been reported to follow IVIG infusion, including cases of myocardial infarction. Of particular importance to transplant recipients is the development of acute renal failure. IVIG products differ in osmolality, pH, and sugar and sodium content. Most preparations of IVIG contain carbohydrate additives such as sucrose or sorbitol, which can induce osmotic injury *(osmotic nephrosis)* to the proximal tubular epithelium. Proximal tubular cells swell and are filled with isometric vacuoles. Patients with impaired baseline renal function may suffer further deterioration of function that may necessitate dialysis and may produce a confusing clinical picture. The tubular injury is self-limited and typically resolves within several days. Patients should be warned of the possibility of transient graft dysfunction, which may be prevented by administration while on dialysis. Practitioners must familiarize themselves with the IVIG preparation available at their institution and to the specific risk profile associated with them.

Humanized Anti-CD25 Monoclonal Antibodies

Mechanism of Action

The anti-CD25 monoclonal antibodies basiliximab and daclizumab are targeted against the α chain (also referred to as CD25, or Tac) of the IL-2 receptor (Plate 5.1). The receptor is up-regulated only on activated T cells (see Chapter 2), and as a result of the binding of the antibody, IL-2-mediated responses are blocked. The anti-CD25 monoclonal antibodies thus complement the effect of the calci-neurin inhibitors, which reduce the production of IL-2. They are designed to prevent, but not treat, episodes of acute rejection.

Basiliximab (Simulect) and *daclizumab* (Zenapax) are two similar compounds that were introduced into clinical transplantation by virtue of their capacity to reduce the incidence of acute rejection episodes when used in combination with cyclosporine and corticosteroids (see Part III). They both originate as murine monoclonal antibodies, which are then genetically engineered so that large parts of the molecule are replaced by human IgG.

The resulting compounds have low *immunogenicity* because they do not induce production of significant amounts of human antimurine antibody. As a result, they have a prolonged half-life in the peripheral blood, and they do not induce a first-dose

reaction. The compounds thus differ from the fully xenogeneic OKT3, which has a short half-life, generates a strong antimurine response, and has a pronounced first-dose reaction. In the case of basiliximab, the entire variable region of the murine antibody remains intact, whereas the constant region originates from human IgG; the resulting compound is strictly deemed *chimeric* and is of 75% human and 25% murine origin. In the case of daclizumab, only the antibody-binding site is of murine origin, and the resulting compound is deemed *humanized* and is of 90% human and 10% murine origin. This discrete difference between the compounds accounts for the fact that the affinity of basiliximab for the IL-2 receptor is greater than the affinity of daclizumab for the receptor. This difference appears to have little clinical significance but explains why the dose of daclizumab is greater than the dose of basiliximab.

Dose and Administration

The immunosuppressive potency of both drugs is presumed to be related to their capacity to produce complete and consistent binding to the IL-2 receptor α sites on T cells. Both drugs have a half-life of longer than 7 days, which permits a long dosage interval. The dosing protocols used in the clinical trials leading to their introduction into clinical transplantation were designed to

---

produce binding of the receptor sites during the early post-transplantation period when the incidence of acute rejection episodes is highest. In the case of basiliximab, two intravenous doses of 20 mg are given, the first dose preopera-tively and the second dose on postoperative day 4; this regimen produces saturation of the IL-2α receptor sites for 30 to 45 days. In the case of daclizumab, the package insert requires that five doses of 1 mg/kg are given, starting preoperatively and then at 2-week intervals, producing saturation of the IL-2α sites for up to 12 weeks. A two-dose course of daclizumab is used by most programs and appears to be effective.

Side Effects

Both drugs are remarkable by virtue of the absence of significant side effects. Anaphylaxis or first-dose reactions are essentially absent with daclizumab but have occasionally been described with basiliximab. In the clinical trials leading to their introduction, the incidence of typical transplant-related side effects was not greater in the treatment groups than in the control groups.

Rituximab

Rituximab (Rituxan) is a monoclonal antibody directed against the CD20 antigen on B lymphocytes. A rapid and sustained depletion of circulating and tissue-based B cells follows its intravenous administration. B-cell recovery begins about 6 months after completion of treatment. Rituximab is approved for use in the treatment of certain forms of non-Hodgkin lymphoma. It has also been used in a variety of presumed

autoimmune diseases to suppress antibody formation. In clinical transplantation, it has been used off-label in a variety of ways: in an attempt to reduce high levels of preformed anti-HLA antigens; to facilitate living donor transplantation in the face of a positive crossmatch or ABO incompatibility; to treat acute humoral rejection; to treat recurrent post-transplantation focal and segmental glomerulosclerosis; and to treat post-transplantation lymphopro-liferative disease, which is usually $CD20^{+}$ (see Chapter 10). The standard dosage is 375 mg/m^2. Transient hypotension may occur during infusion. Premedication with acetaminophen and diphenhydramine is advisable. Rare cases of PML have been associated with its use. The reader should refer to the package insert for precise dosing and administration guidelines.

PART III. CLINICAL TRIALS AND NEW IMMUNOSUPPRESSIVE AGENTS

During the 1990s, a series of promising new immunosuppressive agents underwent laboratory and clinical evaluation in a successful attempt to broaden and improve the immunosuppressive therapeutic armamentarium; these included tacrolimus, MMF, sirolimus, and the anti-CD25 monoclonal antibodies. Other than the off-label use of the drugs noted above, no major new drug has been introduced into routine clinical transplantation practice. Several promising new immunosuppressive candidates are at various stages of development. The race for their introduction into clinical transplantation practice can be likened to an obstacle course. Some drugs are close to passing the finishing line (e.g., belata-cept; see below), and others (e.g., FTY720, FK778, efalizumab) have faltered and fallen from consideration of use in organ transplantation usually because of unanticipated side effects manifesting in advanced clinical trials.

The great success of organ transplantation that was achieved in the 1990s with currently available agents is, paradoxically, making it exceedingly difficult (and enormously expensive) to prove the added benefit of new agents. In clinical trials of new agents, as discussed later, the use of the traditional marker of drug or protocol superiority—patient or graft survival—proved to be impractical and has largely been replaced by alternative end points.

CLINICAL TRIALS

Before any clinical trials can be performed with an investigational agent, an *investigational new drug* (IND) application has to be submitted to the FDA or to an equivalent regulatory body outside of the United States. Approval of the IND application is based on the evaluation of preclinical studies that suggest potential therapeutic benefits of a new agent and on the evaluation of studies in a variety of animals that suggest its safety. Phase 1 clinical studies are performed in healthy human volunteers or patients to evaluate human metabolism, pharmacokinetics, dosage,

safety, and, if possible, effectiveness. Phase 2 includes controlled, open-label, clinical studies conducted to evaluate the effectiveness of the drug for a particular indication and to determine dose regimens, common side effects, and risks. Phase 3 studies are expanded trials based on preliminary evidence from the previous phases that suggest efficacy and safety. They are sometimes called *pivotal trials* because they are critical for FDA-approved licensing and registration. They typically involve large, usually *multicenter,* clinical trials that are *randomized* and, if possible, *double-blinded* using *placebo controls*. These studies serve to refine dosage, determine benefit, and further evaluate the overall risk-to-benefit ratio of the new drug. In organ transplantation, particular care has to be taken to ensure that any potential benefit of a new agent is not outweighed by the consequences of too much immunosuppression or by organ-specific toxicity. Successful completion of phase 3 should provide an adequate basis for product labeling and permit approval of the drug for its defined indications. Following introduction of a new drug into the clinical marketplace, phase 4 studies may be performed under the auspices of the manufacturer or of independent investigators or at the request of the FDA to further refine the role of the drug in clinical practice.

Any human use of an experimental drug is strictly governed by the predetermined rules of the experimental protocol under which the drug is administered. Patients must read, understand, and sign an informed consent form that clearly defines the nature of the experiment in which they are involved and its potential risks and benefits. They must also receive a copy of the *patient's bill of rights,* which clearly defines the nature of their commitment, and authorize the release of personal health information according to the provision of federal privacy laws [the Health Insurance Portability and Accountability Act (HIPAA)]. The experimental protocol and consent form must have been approved by an *institutional review board* (IRB) or *human subjects protection committee* (HSPC), and the medical staff administering the protocol must feel totally comfortable with it. After a drug is licensed, it is often used off-label for indications, or in doses, different from those precisely defined. Such use does not require a formal consent procedure, although it is wise to inform the patient that the drug is being given for an unapproved use.

Clinical Trial Design in Transplantation

Immunosuppressive practitioners must understand the way in which new agents are introduced because clinical trials of new immunosuppressive agents not only have led to their clinical use but also have largely determined the way in which these agents are used. It is also particularly important to appreciate what primary *end points* were used to determine the efficacy of the new agents. The choice of primary end point, the frequency with which this end point occurs in the control population, and the anticipated capacity of the new agent to change the incidence of the end point (estimated from phase 2 studies) permit a statistical evaluation of the number of patients required to be enrolled in the study so that the study has sufficient statistical power to determine the effectiveness of the new agent. Secondary end points usually

include side-effect comparisons, renal function estimations, and long-term effects on patient and

graft survival. Studies may not have the *statistical power* to provide answers to the questions posed by the secondary end points.

When the clinical trials for cyclosporine use in kidney transplantation were designed in the late 1970s and early 1980s, the primary end point used was improvement of patient and graft survival, which cyclosporine indeed achieved. Tacrolimus was introduced based on its capacity to produce results equivalent to cyclosporine. OKT3 was introduced based on its superior capacity, when compared with corticosteroids, to reverse episodes of acute rejection, and Thymoglobulin was introduced for its superiority in reversing acute rejection when compared with Atgam. All the remaining available new drugs (MMF, sirolimus, anti-CD25 monoclonal antibodies) have been introduced based on their capacity, when combined with cyclosporine and prednisone, to reduce the incidence of acute rejection episodes.

End Point for Studies of New Immunosuppressive Drugs

The incidence of acute rejection episodes, typically biopsy proven (see Chapter 14), has become the most frequently used marker of the effectiveness of new immunosuppressive drugs for the following reasons:

1. Because of the excellent results of kidney transplantation with currently available immunosuppressants, with 1-year graft survival rates of greater than 90% in most centers and minimal mortality, it is statistically extremely difficult to prove the benefit of new agents or protocols in terms of patient or graft survival.

2. Acute rejection is a potent risk factor for the development of chronic allograft failure (see Chapter 10). In retrospective analyses, patients who have suffered episodes of acute rejection have a long-term graft survival rate that is 20% to 30% less than the graft survival rate of patients who have not suffered acute rejection.

3. Acute rejection episodes are morbid events in themselves, requiring intensification of immunosuppression and sometimes hospital admission.

4. Most acute rejection episodes take place within the first few months of transplantation, and their presence can be proved on biopsy. This permits a rapid evaluation of the effectiveness of a new agent or protocol (a luxury that is not available when immunosuppressive drug trials are performed in other clinical circumstances, such as systemic lupus erythematosus or rheumatoid arthritis).

Figure 5.5 provides an example of the way in which the incidence of biopsy-proven acute rejection episodes is used to show the effectiveness of a new agent from one of the pivotal trials leading to the introduction of MMF in the mid-1990s. This trial was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study to evaluate the efficacy of MMF for the prevention of acute rejection episodes during the first 6

months after transplantation. In this trial, standard therapy consisted of cyclosporine, prednisone, and azathio-prine. The study compared two doses of MMF (1.0 g given twice daily and 1.5 g given twice daily) or azathioprine in combination with cyclosporine and prednisone. Figure 5.5 illustrates the clear-cut benefit of MMF with respect to the primary end point. There was a statistically significant reduction in the incidence of acute rejection episodes from 41% in the azathioprine group to about 20% in both the MMF groups. There was no statistically significant benefit of MMF with respect to patient or graft survival when estimated at either 1 or 3 years.

A statistically significant reduction in the incidence of acute rejection episodes was also achieved in the pivotal clinical trials leading to the introduction of sirolimus and the anti-CD25 monoclonal antibodies. A significant effect on patient and graft survival was not achieved, probably because the studies did not have the statistical power to show such an effect.

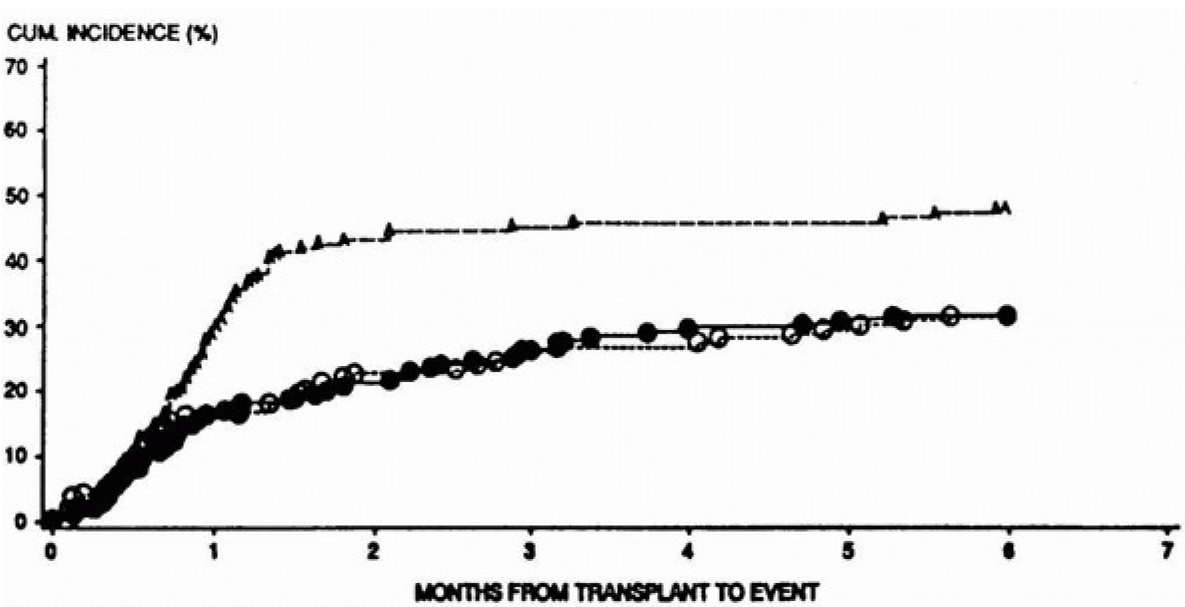


FIGURE 5.5 Effects of mycophenolate mofetil on the cumulative incidence of biopsy-proven acute rejection and treatment failure during the first 6 months after transplantation. A, azathioprine group; 0, mycophenolate mofetil, 1.0 g bid; •, mycophenolate mofetil, 1.5 g bid. (From Sollinger HW, for the U.S. Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. Transplantation 1995;60:225-232, with permission.)

As new immunosuppressive drugs and protocols are introduced and the incidence of acute rejection decreases, it is becoming increasingly difficult to prove the statistically significant benefit of newer drugs. In the pivotal trials leading to the introduction of MMF, sirolimus, and the anti-CD25 monoclonal antibodies, the incidence of acute

rejection in the patients receiving the experimental drug protocol was compared with the incidence of acute rejection in patients receiving *standard therapy* with cyclosporine, prednisone, and azathioprine. The success of MMF in reducing the incidence of acute rejection led to it becoming part of an updated standard therapy protocol in many centers (see Part IV). As a result, for trials of newer agents, statistical proof of further reduction in the incidence of acute rejection will likely be more difficult to achieve. In current and future trials, end points may be based on functional parameters such as estimates of renal function, on histologic parameters such as scores for chronic allograft injury (see Chapter 14), on immune parameters (see Chapter 2), or on a composite of multiple end points.

The phased evaluation of new drugs discussed above is designed primarily to lead to the introduction by pharmaceutical manufacturers of individual new agents that are safe and efficacious. These trials, however, may not address the clinical questions posed by practitioners who are more concerned with the safety and effectiveness of drug combinations. The comparison groups in formal registration trials are previously approved protocols that often do not represent "standard of practice" at the time the trials are complete—hence their information may be of limited practical value to practitioners. Postregistration trials often describe single-center experience, and the clinical value of retrospective database analyses is intrinsically limited. Large, multicenter, randomized trials such as the CAESAR, ELITE-Symphony, and CONVERT trials discussed in Part IV attempt to evaluate immunosuppressive drug protocols in a manner that addresses these concerns.

New Immunosuppressive Drugs

Multiple new drugs and therapeutic concepts are at different stages of development. Those drugs that are in advanced clinical trials and show promise of

---

introduction into the clinical *arena are* discussed below (refer to Vincenti and Kirk in "Selected Readings").

Belatacept

Optimal and sustained T-cell response after antigen recognition (signal 1) requires costimulatory signals (signal 2) delivered through accessory T-cell surface molecules (see Chapter 2 and Plate 5.1). The best understood and therapeutically relevant costimulatory pathway is CD28:B7. Cytotoxic T-lymphocyte antigen-4 immunoglobulin (CTLA-4-Ig) is a humanized fusion protein, a homo-logue of CD28, which binds the B7 molecule with high affinity and blocks the interaction with CD28. Used alone or in combination, it prevents rejection in small animal models and nonhuman primates.

Abatacept and belatacept are two forms of CTLA-4-Ig with different degrees of competitive affinity for the B7 receptor. Abatacept is approved for treatment of rheumatoid arthritis. Belatacept is a second generation abatacept with a higher

affinity. Phase 2 trials have shown that the drug, when used in combination with MMF, basiliximab, and corticosteroids, permits safe avoidance of calcineurin inhibitors. Renal function and metabolic parameters were improved for patients receiving belatacept compared with those receiving cyclosporine.

Several large international phase 3 trials of belatacept are in progress. In the most advanced of these, belatacept is administered in an intravenous injection in low-intensity and high-intensity protocols (injection frequency varying from 4 to 8 weeks) to patients receiving extended criteria donor kidneys and kidneys deemed susceptible to delayed graft function (see Chapter 4) in one study and living donor and standard criteria donor kidneys in another. MMF and low-dose steroids are also given in the experimental group: the experimental groups receive “standard therapy” with cyclosporine, MMF, and low-dose steroids. Preliminary results in these studies suggest excellent patient and graft outcomes in the experimental group with improved GFR compared with controls despite a higher incidence of acute rejection. Metabolic parameters were also more favorable in the experimental group. The overall incidence of posttransplantation lymphoproliferative disease has been about 1% in all the belatacept studies.

If belatacept is approved for clinical use in kidney transplantation, it will offer a radically different therapeutic paradigm. Monthly intravenous injections may replace use of calcineurin inhibitors and their drug-level monitoring. A subcutaneously administered form of belatacept is in development.

Other Monoclonal Antibodies

Efalizumab (Raptiva) is a humanized CDlla-specific IgG1 targeted against the lymphocyte-associated function-1 (LFA-1) molecule. LFA-1 binds to intercellular adhesion molecules, and the interaction is important in the recruitment of leukocytes to the sites of inflammation (see Chapter 2 and Fig. 2.6) and in stabilizing the interaction between T cells and APCs. Efalizumab has been approved for the treatment of severe psoriasis and was being developed for use in transplantation as a subcutaneously administered immunosuppressant in calcineurin inhibitor-free protocols. Phase 1 and 2 studies show the drug to be effective, although in high doses, there was an increased incidence of PTLD. Cases of PML were reported in patients with psoriasis, and the FDA has halted its development for transplantation in the United States.

Alefacept (Amevive) is a humanized LFA-3-IgG1 fusion protein that binds to CD2 on T lymphocytes and blocks the interaction between LFA-3 and CD2 and interferes with T-cell activation. It has been approved for use in psoriasis. Phase 2 studies are in progress.

Janus Kinase and Protein Kinase Inhibitors

Janus Kinases (JAKs) are a family of cytoplasmic tyrosine kinases involved in cell surface signaling. JAK-3 (CP-690550) is being evaluated in clinical trials and appears to be an effective immunosuppressant, although high doses have been associated with an increase risk for infections. AEB 071 is a protein kinase inhibitor whose development for use in a calcineurin inhibitor protocol was discontinued because of treatment failure but is been developed in Europe in combination with everolimus. Phase 3 trials in the United States are under consideration.

Bortezomib

Bortezomib (Velcade) is a proteosomal inhibitor that is FDA approved for the treatment of multiple myeloma. The immune-modulating affects of the drug are pleiotropic and result, in part, from its proapoptotic effects on plasma cells. Bortezomib also suppresses T-cell function, and the drug has potential for the treatment and prevention of both antibody-mediated and cell-mediated rejection. Preliminary studies suggest that the drug is effective and safe and that it reduces levels of donor-specific antibodies (DSAs; see Chapter 3). DSAs are increasingly thought to be an important cause of chronic rejection and graft loss, and if bortezomib is shown to be able to reduce or remove them over the long term, it may provide a valuable means to prolong graft function.

Immune Modulation and Tolerance Induction

Immune modulation is a somewhat vague term used to describe attempts to modify the immune response in a nonspecific fashion in order to facilitate allograft acceptance without impairing effector cells or mechanisms. Several techniques fall within this category. Infusion of *donor-specific bone marrow* or *stem cells,* or *total lymphoid irradiation,* in combination with short-term nonspecific immunosuppression, has produced long-term graft survival in the absence of immunosuppressive therapy in experimental and clinical organ allografts. The donor bone marrow provides an as yet unidentified signal for tolerance. *Blood transfusions* are known to exert beneficial effects on animal and human allograft survival through a variety of potential mechanisms. The tolerogenic effect of bone marrow and blood may also be a result of the development of a state of microchimerism (see Chapter 2). A randomized trial of perioperative donor-specific blood transfusions in live donor transplants showed no practical benefit. Although some success has been achieved with these innovative techniques, they all require heavy initial immunosuppression, and there is often evidence of residual immune response. They are not yet ready for broad clinical application.

PART IV. IMMUNOSUPPRESSIVE PROTOCOLS

GENERAL PRINCIPLES OF PROTOCOL DESIGN

The variety of immunosuppressive drugs available for use in clinical transplantation permits permutations that make up immunosuppressive protocols. Transplant centers tend to be loyal to their own protocols, which have often been developed in response to local needs and experience. Financial considerations, both for patients and institutions, may determine the choice between similar agents. Protocols should be regarded as guides for therapy that need not necessarily be adhered to slavishly. They may require modification from patient to patient with new knowledge and experience. In an era in which short-term success rates for deceased donor transplantation of greater than 90% are commonplace, it may take experience with hundreds of patients followed for prolonged periods to prove the benefit of a new or modified approach.

There are limited prospective data on the effects of different protocols on 5- and 10-year graft survival. Most of the data on long-term protocol design come from retrospective analysis and analysis of large databases. Although valuable, these analyses bring with them intrinsic design flaws. For instance, in a prospective blinded study, it is possible to ensure that the groups that are compared are demographically and clinically similar and that investigator bias in the choice of protocol is negated. In database analyses, such assurances are absent, and analyses are limited by the reliability of the data that are entered. Database analyses, however, permit evaluation of a very large number of patients over a prolonged period and may permit recognition of trends and associations not noted in short-term prospective studies on a limited number of patients. The relevance to individual patients of outcome studies based on database analysis must be considered with circumspection.

Table 5.6 lists the components of a conventional immunosuppressive protocol. These components are relevant to all recipients with the possible exception of two-haplotype-matched living related donors. The broad range of immunosuppressive drugs now available has also led to the development of a series of innovative protocols. In some programs, innovative protocols have become the local standard of therapy. For all protocols, because the risk for acute rejection is highest in the first weeks and months after transplantation *(induction phase)* and diminishes thereafter *(maintenance phase)*, immunosuppression should be at its highest level in this early period and should be reduced for long-term therapy. The most feared side effects of immunosuppression—opportunistic infection and malignancy—tend to reflect the total amount of immunosuppression given rather than the dose of a single drug. The total quantity of immunosuppression should thus be monitored and considered in all stages of the post-transplantation course.

CONVENTIONAL IMMUNOSUPPRESSIVE PROTOCOLS

Conventional immunosuppressive protocols consist of a calcineurin inhibitor, an adjunctive agent, corticosteroids, and the possible addition of antibody induction. With conventional protocols, most programs are able to achieve 90% to 95% graft survival

with an acute rejection rate of 10% to 20%.

Cyclosporine or Tacrolimus?

Calcineurin inhibitors remain the backbone of transplant immunosuppression and are likely to remain so until such time as similarly effective but less toxic—in particular, nephrotoxic—agents are introduced into clinical practice.

Although much has been made of discrete differences between cyclosporine and tacrolimus, the fact is that these drugs are remarkably similar, and both are highly effective. Table 5.1 summarizes their similarities and differences. These differences may guide the choice of agent in individual patients. For example, cyclosporine may be preferred in some centers for African American patients because of the increased incidence of post-transplantation glucose intolerance in patients who receive tacrolimus; tacrolimus may be preferred in adolescents and other patients who are concerned about cosmetics because of the more marked cosmetic changes associated with cyclosporine; cyclosporine may be preferred in some patients because of the generally milder neurologic side effects; tacrolimus may be preferred in recipients of simultaneous kidney and pancreas transplants because of its somewhat greater immunosuppressive potency despite its greater islet toxicity (see Chapter 15); tacrolimus-induced hair loss in adult females may prompt conversion to cyclosporine.

TABLE 5.6 Components of the Conventional Immunosuppressive Protocol

Class of Agent	Options
Calcineurin inhibitor	Cyclosporine, tacrolimus
Corticosteroids	Dose and regimen
Adjunctive agent	Azathioprine, MMF, sirolimus

Antibody induction	Lymphocyte depleting or nondepleting
Supplementary agents	CCB, HCRI
Infection prophylaxis	Bactrim, antivirals

CCB, calcium channel blocker; HCRI, HMG-CoA reductase inhibitor; MMF, mycophenolate mofetil.

Prospective data comparing the two drugs have tended to favor tacrolimus. These studies are often difficult to interpret, however, because of protocol design and the introduction of improved formulations and drug-level monitoring of cyclosporine. There has been a steady trend during the past decade toward greater use of tacrolimus. In the United States, about 80% of patients receive tacrolimus at the time of discharge from hospital, and most of the remainder receive cyclosporine. A similar trend has been observed in Europe.

Which Adjunctive Agent?

In this discussion, the term *adjunctive agent* is used to describe the immunosuppressive drugs that are used in combination with a calcineurin inhibitor in the early post-transplantation period to enhance the potency of the immunosuppressive protocol as reflected by a decreased incidence of acute rejection episodes. Most programs continue to use combination therapy over the long term. Aza-thioprine has been replaced by MMF or enteric-coated MPA (most commonly MMF) in most centers because of its superior capacity to reduce the incidence of acute rejection (Fig. 5.5) and evidence, that has been the subject of some controversy, that long-term outcomes are also improved. The MMF-MPA combination with tacrolimus is used in about 80% of patients in the United States.

Sirolimus became available for clinical use in late 1999. In its initial U.S. package insert, it was used in a manner similar to MMF with a full-dose of the calcineurin inhibitor and a fixed sirolimus dose. It is now rarely used this way, and drug-level monitoring of sirolimus is regarded as mandatory for optimal use, typically with attenuated doses of calcineurin inhibitor. Because of the side-effect profile of sirolimus

and the failure to show superiority over MMF in most clinical circumstances (see discussion of Symphony trial, below), it is used as a primary agent in less than 10% of cases in the United States. Sirolimus may be of particular value in patients deemed to be at high risk for post-transplantation malignancy or those who develop *de novo* malignancy after transplantation (see Chapter 10).

Antibody Induction

Antibody induction is the term used to describe the use of the depleting antibodies (OKT3, Thymoglobulin, alemtuzumab) or one of the nondepleting anti-CD25 monoclonal antibodies (basiliximab, daclizumab) in the first 2 weeks after transplantation. OKT3 is now rarely used, and when Thymoglobulin is given, the calcineurin inhibitor is withheld or its dose is reduced until 2 to 3 days before the antibody course is completed. Induction protocols with Thymoglobulin are an alternative to the use of a calcineurin inhibitor in the early posttransplantation period and are therefore different from induction using one of

---

the nondepleting antibodies, in which concomitant use of a calcineurin inhibitor is recommended. In *sequential* therapy, Thymoglobulin is administered and the calcineurin inhibitor is introduced only when renal function has reached a predetermined level (e.g., a plasma creatinine level of 3 mg/dL). The antibody is discontinued as soon as adequate calcineurin inhibitor levels are achieved. A patient with a well-functioning graft may thus receive only a few days of antibody treatment.

Table 5.7 lists the advantages and disadvantages of depletional antibody induction. The benefits of Thymoglobulin and alemtuzumab induction have not been compared directly in a systematic fashion, but available data suggest a similar degree of effectiveness. There remains much discussion regarding the relative benefits of Thymoglobulin and the anti-CD25 monoclonals. For low-risk patients, they are as effective as the depletional agents. A prospective trial of the two forms of induction in high-risk recipients (see “High-Risk and Low-Risk Groups,” below) was discontinued because of an apparent benefit of Thymoglobulin. This benefit, however, was not recognized in a retrospective analysis. Long-term retrospective studies have not shown significant benefit of routine induction therapy in terms of patient and graft survival.

In many programs, depletional antibody induction is reserved for immunologically high-risk recipients or for patients in whom delayed graft function is anticipated. Depletional antibody induction may also be indicated for patients requiring anticonvulsant drugs that may make it difficult to achieve therapeutic levels of calcineurin inhibitors in the early post-transplantation period. In the United States, about 75% of patients receive some form of antibody induction, most frequently Thymoglobulin.

High-Risk and Low-Risk Groups

All patients are not equal with respect to the chances of rejection or graft loss, and

protocols should be individualized to take this into account. Patients undergoing simultaneous kidney-pancreas transplantation and patients with high levels of preformed antibodies or previously failed transplants may require more intense therapy. Patients with delayed graft function have an increased susceptibility to episodes of acute rejection. In several clinical trials, African American patients have required higher doses of immunosuppressive drugs to achieve the same immunosuppressive benefit, and some programs take this into account

routinely in protocol design. Young patients tend to be immunologically aggressive; protocol design for children is discussed in Chapter 16. Older patients may not tolerate heavy immunosuppression, and kidneys from older donors may be less tolerant of immunologic and other insults. Recipients of transplants from well-matched deceased donors or from living related donors, particularly from two-haplotype-matched donors, may require less immunosuppression.

TABLE 5.7 Potential Advantages and Disadvantages of Depleting Antibody Induction

Potential Advantages
Improved graft survival for high-risk patients
Period of delayed graft function may be foreshortened
Onset of first rejection is delayed
Obviates early use of calcineurin inhibitor
May permit less aggressive maintenance regimen

Potential Disadvantages

Risk for first-dose reactions

May prolong hospital admission stay

Greater cost

Higher incidence of cytomegalovirus infection

Increased short- and long-term mortality reported

How Long to Continue Immunosuppression?

The immune system has a long memory! Immunosuppression is required for the functional life of the graft, even if it has lasted two decades or more. Discontinuation of immunosuppressive drugs, even many years after transplantation, may lead to late acute rejection or accelerated chronic rejection. In stable patients, carefully monitored reduction or even discontinuation of individual components of the immunosuppressive protocol may be safe.

When to Stop Immunosuppression?

The minimal mortality that is now associated with kidney transplantation is to a large degree the result of an appreciation of when to minimize or stop immunosuppression and abandon a kidney. Discontinuation of immunosuppression may be necessary for patients with resistant opportunistic infection or malignancy (see Chapters 10 and 11). Patients with deteriorating graft function despite more than two or three appropriately

treated rejections are better allowed to return to dialysis and seek another transplant. With the constant introduction of new immunosuppressive agents into clinical practice, great care and judgment are needed to avoid the temptation of excessively adding or exchanging new agents.

SPECIFIC PROTOCOL RECOMMENDATIONS

Cyclosporine

Cyclosporine, 6 to 10 mg/kg per day orally, is given as a single dose or twice daily starting immediately before transplantation or on the first postoperative day. Cyclosporine can be administered by intravenous infusion over 4 hours or can be given as a constant infusion over 24 hours; the dose is one third of the oral dose. For patients who receive depleting antibody induction, oral cyclosporine is usually started several days before the completion of the course of therapy so that drug levels will be therapeutic at the time of the final antibody dose. Doses are then adjusted to maintain levels within the ranges given in Table 5.8. It is wise to continue to monitor levels of cyclosporine, although the degree of reliance on these levels and the frequency of their measurement vary from program to program. The desired dose and target levels are influenced by the concomitant use of adjunctive agents and history of rejections. By 3 months after transplantation, most patients are receiving cyclosporine in a dose of 3 to 5 mg/kg per day.

There is still no clear consensus regarding the best dose or drug level for long-term cyclosporine use, and it is unfortunate that prospective randomized trials comparing cyclosporine dose ranges are not available. Drug-level monitoring with 2-hour (C2) peak levels may be more effective than trough-level monitoring. Recommended peak levels have not been extensively validated with varied transplant populations and protocols, and the recommended levels noted in Table 5.8 should be considered accordingly. Fear of progressive nephrotoxicity has tempted many clinicians to permit low levels, yet such a policy may allow for the insidious development of chronic rejection. Retrospective studies show that continued use of cyclosporine is conducive to prolonged adequate graft function.

TABLE 5.8 Approximate Therapeutic Ranges for Cyclosporine

Post-transplantation Month	HPLC and EMIT (ng/mL)	FPIA (ng/mL)	C2 levels* (μg/mL)

0-2[†]	150-350	250-450	1.2-1.5
2-6	100-250	175-350	0.8-1.2
>6	~100	~150	0.5-0.8

EMIT, enzyme-multiplied immunoassay technique; FPIA, fluorescent polarization immunoassay; HPLC, high-performance liquid chromatography.

[*] Drawn within 15 minutes of 2 hours postdose. For C2 levels, no change in target levels is required for different assay types.

[†] In the first few days after transplantation, the trough cyclosporine level should not fall below 300 ng/mL by HPLC.

Which Cyclosporine Formulation?

Most patients are started and maintained on Neoral. Patients who were started on Sandimmune may choose to switch from Sandimmune to Neoral, although there is no overriding medical reason to do so. The switch requires care because of the different pharmacokinetics of the two formulations (see “Cyclosporine” under “Formulations and Pharmacokinetics,” above). Although a 1:1 dose ratio is recommended, some patients require somewhat less Neoral than Sandimmune. Even in stable patients, cyclosporine blood levels should be monitored more carefully in the month after the switch and dose adjustments made. An elevation of the creatinine level soon after a switch is more likely to be a result of nephrotoxicity than of rejection. The decision to use a generic formulation is a financial rather than a medical one. Any switching of formulations requires careful monitoring because the pharmacokinetic parameters of the generic formulations may differ.

Tacrolimus

The recommended starting dose of oral tacrolimus is 0.15 to 0.30 mg/kg per day administered in a split dose every 12 hours. Intravenous tacrolimus is rarely required in kidney transplantation. Doses are adjusted to maintain tacrolimus drug levels at between 10 and 15 ng/dL during the first few post-transplantation weeks and somewhat lower thereafter. There is marked patient-to-patient variation in the dose of tacrolimus required to achieve these levels, with some patients receiving as little as 2 mg daily and some patients receiving 10 times that dose. The relationship between drug levels and manifestations of toxicity varies considerably among patients.

Switching Calcineurin Inhibitors

If side effects develop with one of the calcineurin inhibitors, it is quite reasonable to switch to the other agent. Common reasons for switching are cosmetic (tacrolimus to cyclosporine for hair loss and the converse for hirsutism; cyclosporine to tacrolimus for gingival hypertrophy). In some patients, new-onset diabetes mellitus (see Chapter 10) may respond to conversion from tacrolimus to cyclosporine. The dose chosen at the time of switching must be individualized. There is no need to overlap the drugs, and steroid “coverage” is usually unnecessary. Patients should be monitored carefully after switching.

Corticosteroids

The use of corticosteroids in the peritransplantation period has been dramatically reduced in the past decade (discussed later). A large dose of methylpred-nisolone is still typically given intraoperatively in a dose of up to 1 g. In standard protocols, the dose is then reduced rapidly from 150 mg on day 1 to 20 mg on day 14. Some programs avoid the steroid cycle altogether, modifying it or starting at 30 mg daily or even less. The maximal oral dose of prednisone at 1 month should be 20 mg, and 10 mg at 3 months. The long-term maintenance dose should not be greater than 10 mg daily, and in most programs, it is 5 mg daily. Rejection episodes may occasionally occur when even very small dose reductions are made. High maintenance dose protocols of steroids sometimes used for collagen vascular disease and vasculitides are unnecessary and contraindicated in kidney transplantation.

Adjunctive Agents

The standard dose of MMF in adults is 1000 mg twice daily, although African American patients may benefit from a higher dose (1500 mg twice daily) in the early post-transplantation period. Patients on full-dose tacrolimus may require a lower dose. Some evidence suggests that measurement of mycophenolic acid AUC may be useful in predicting the effectiveness of MMF; however, the more convenient trough levels have

not been convincingly shown to be useful and are generally not measured. If the dose of MMF is reduced or held for short periods in the event of side effects, the dose of calcineurin inhibitor and prednisone should be maintained. The longer the MMF dose is reduced, the greater is the risk for subsequent rejection, and patients should be monitored accordingly. Most programs continue to administer MMF for prolonged periods; administration for at least 1 year has been shown, in retrospective studies, to produce measurable benefit in graft survival and to reduce the incidence of late acute rejections.

The maintenance dose of sirolimus is typically 2 to 5 mg once daily with target blood levels similar to those described for tacrolimus (see "Tacrolimus," above). If the accompanying calcineurin inhibitor is totally discontinued, the dose requirements of sirolimus to maintain adequate levels may increase. The standard recommended dose of sirolimus is 2 mg administered once daily 4 hours after the morning dose of cyclosporine although many patients take the two drugs simultaneously. If sirolimus is to be the primary agent, a loading dose of 6 mg is given on the first day of treatment to accelerate the achievement of a stable trough level. African American patients may require a higher dosage. Trough drug-level monitoring is now routine. If sirolimus is given with tacrolimus, a combined trough level of about 15 ng/dL is typically adequate. Sirolimus administration should be accompanied by low-dose prophylaxis with Bactrim for at least 1 year.

The inclusion of *calcium channel blockers,* usually either diltiazem or verapamil, in the standard immunosuppressive regimen has several potential advantages. In addition to their antihypertensive properties, both drugs may minimize calcineurin inhibitor-induced vasoconstriction and protect against ischemic graft injury and nephrotoxicity. Both drugs compete with the calcineurin inhibitors for excretion by the P-450 enzyme system, raising drug levels and permitting safe administration of lower doses. Calcium channel blockers may also possess some intrinsic immunomodulatory activity of their own related to the role of cytosolic calcium levels or gene activation. The routine inclusion of calcium channel blockers in the post-transplantation protocol may improve 1-year graft survival rates by 5% to 10%.

Protocols for Living Donor Transplants

Excellent results were achieved for two-haplotype-matched living related transplants immunosuppressed with azathioprine and prednisone alone before the introduction of cyclosporine into routine clinical practice. Despite this experience, most transplantation programs now use calcineurin inhibitor-based protocols for these patients because of the lesser incidence of acute rejection. Two-haplotype-matched transplant recipients receiving calcineurin inhibitors may be good candidates for steroid avoidance or withdrawal. MMF can potentially be used to replace the calcineurin inhibitor. For all other living donor transplants, conventional protocols are

calcineurin inhibitor based and are similar to those described for deceased donor transplants. Routine lymphocyte-depleting antibody induction is not required, and some programs dispense with antibody induction altogether.

Low-Cost Protocols

The immunosuppressive drugs and protocols described above are expensive to a degree that may preclude transplantation in the developing world, or for those without adequate health insurance and drug cost coverage in the developed world. In the developing world, most transplants are from living donors in unsensitized recipients. In these circumstances, excellent results can be achieved without using antibody induction and with the less expensive generic preparations of calcineurin inhibitors combined with azathioprine and low-dose steroids, both of which are inexpensive. The dose of azathioprine is 1 to 3 mg/kg. Drug levels are not measured, and the dose is usually fixed with adjustments made for hematologic toxicity. For patients who cannot afford long-term maintenance therapy with MMF or sirolimus, azathioprine is a far better alternative to no immunosuppression at all. The annual cost of azathioprine is about $600, compared with $6000 for MMF.

INNOVATIVE TRANSPLANTATION PROTOCOLS

The availability of multiple immunosuppressive agents has stimulated attempts to minimize or avoid the most toxic components of the standard protocol. The most obvious targets for such efforts are corticosteroids and the calcineurin inhibitors.

Steroid Withdrawal and Steroid Avoidance

Steroid withdrawal, the discontinuation of steroid administration days, weeks, or months after transplantation, needs to be differentiated from *steroid avoidance,* in which steroids are not administered at all. Steroid withdrawal may be rapid (within a week of transplantation) or delayed. The difference between the two techniques is more than semantic, and there is some evidence that rapid withdrawal may be safer than later steroid withdrawal. Rapid withdrawal may also be safer than total steroid avoidance. Because most of the side effects of steroids are a result of the high doses that are given in the early postoperative period and high-dose maintenance therapy, there is good reason to focus efforts on rapid withdrawal or the use of low-dose maintenance therapy.

Nearly one third of all transplant recipients are discharged from the hospital in the United States without steroids, indicating that steroid avoidance is standard of practice in many programs. Most steroid-free protocols administer antibody induction followed by combinations of a calcineurin inhibitor and sirolimus or MMF. Patients who are withdrawn from steroids may have an increased incidence of acute rejection episodes and some return to steroid use. African American patients and presensitized patients may not be suitable candidates for withdrawal. A clear-cut benefit of withdrawal, in

terms of certain steroid-related side effects (e.g., bone disease, hyperlipidemia), has been difficult

to confirm, presumably because even those patients receiving steroids receive very low doses. Steroid withdrawal in selected patients may be associated with a lower incidence of cardiovascular events. Some evidence suggests that there may be long-term deterioration in graft function after steroid withdrawal. The risks and benefits of steroid withdrawal should be thoroughly reviewed with patients before protocol changes are made.

Calcineurin Inhibitor Avoidance, Withdrawal, and Dose Minimization

Avoidance, or at least minimization, of the nephrotoxic effects of the calcineurin inhibitors is indeed a worthy goal. It is a goal, however, that must be approached with great care. In low-risk patients, protocols avoiding calcineurin inhibitors by using combinations of anti-CD25 monoclonal antibodies, corticosteroids, and MMF, or by using sirolimus alone, reportedly permit excellent graft survival but with an unacceptably high incidence of acute rejection episodes. Some protocols effectively combine sirolimus, MMF, and corticosteroids; dose adjustments resulting from hematologic toxicity are common. Calcineurin avoidance is not standard therapy. A protocol of Thymoglobulin induction followed by phased withdrawal has been proposed but has not gained wide acceptance.

In the CONVERT trial, more than 800 patients, 6 months to 10 years after transplantation, were randomized either to remain on cyclosporine or tacrolimus or be converted to sirolimus. Those patients with an estimated GFR of greater than 40 mL/min did well after conversion. GFR was improved, and the incidence of malignancy was less, although proteinuria was somewhat greater. Rates of rejection and patient and graft survival were similar. Enrollment in the 20- to 40 mL/min GFR stratum was halted prematurely because of a higher incidence of safety end points in the sirolimus conversion arm. In well-functioning grafts, switching from a calcineurin inhibitor to sirolimus represents a potential option, although close monitoring is mandatory.

The CAESAR and ELITE-Symphony Trials

These two ambitious, multicenter, multinational, multiprotocol trials attempt to determine the safety and efficacy of different doses of continuous calcineurin inhibitor administration, or withdrawal, in combination with adjunctive therapy. Readers are recommended to read the full reports of these important trials and the editorial commentary that accompanied them (see “Selected Readings”). The Cyclosporine Avoidance Eliminates Serious Adverse Renal-toxicity (CAESAR) trial was designed to determine whether administration of a reduced dose of cyclosporine (target trough levels 50 to 100 ng/mL), continuously or followed by early withdrawal at 6 months, in

primary renal allograft recipients receiving daclizumab induction, MMF, and steroids, can minimize nephrotoxicity and improve long-term renal function without an unacceptable increase in acute rejection. At 12 months, the incidence biopsy-proven acute rejection was unacceptably high in the withdrawal group (38%) compared with the standard dose and continuous low-dose groups (28% and 25%, respectively). GFR was not different between the low-dose and the cyclosporine withdrawal groups.

The Efficacy Limiting Toxicity Elimination (ELITE)-Symphony trial was designed to assess whether an MMF-based regimen would permit the administration of lower doses of calcineurin inhibitors or sirolimus, yet still maintain an acceptable rate of acute rejection and a favorable tolerability profile. The trial used low-dose maintenance levels of cyclosporine, tacrolimus, or sirolimus from the day of transplantation together with daclizumab and steroids. The most favorable regimens (Fig 5.6), in terms of the incidence of acute rejection, graft survival, renal function, and side-effect profile, were the low-dose

tacrolimus followed by the low-dose cyclosporine regimen (acute rejection incidence 12% and 24%, respectively).

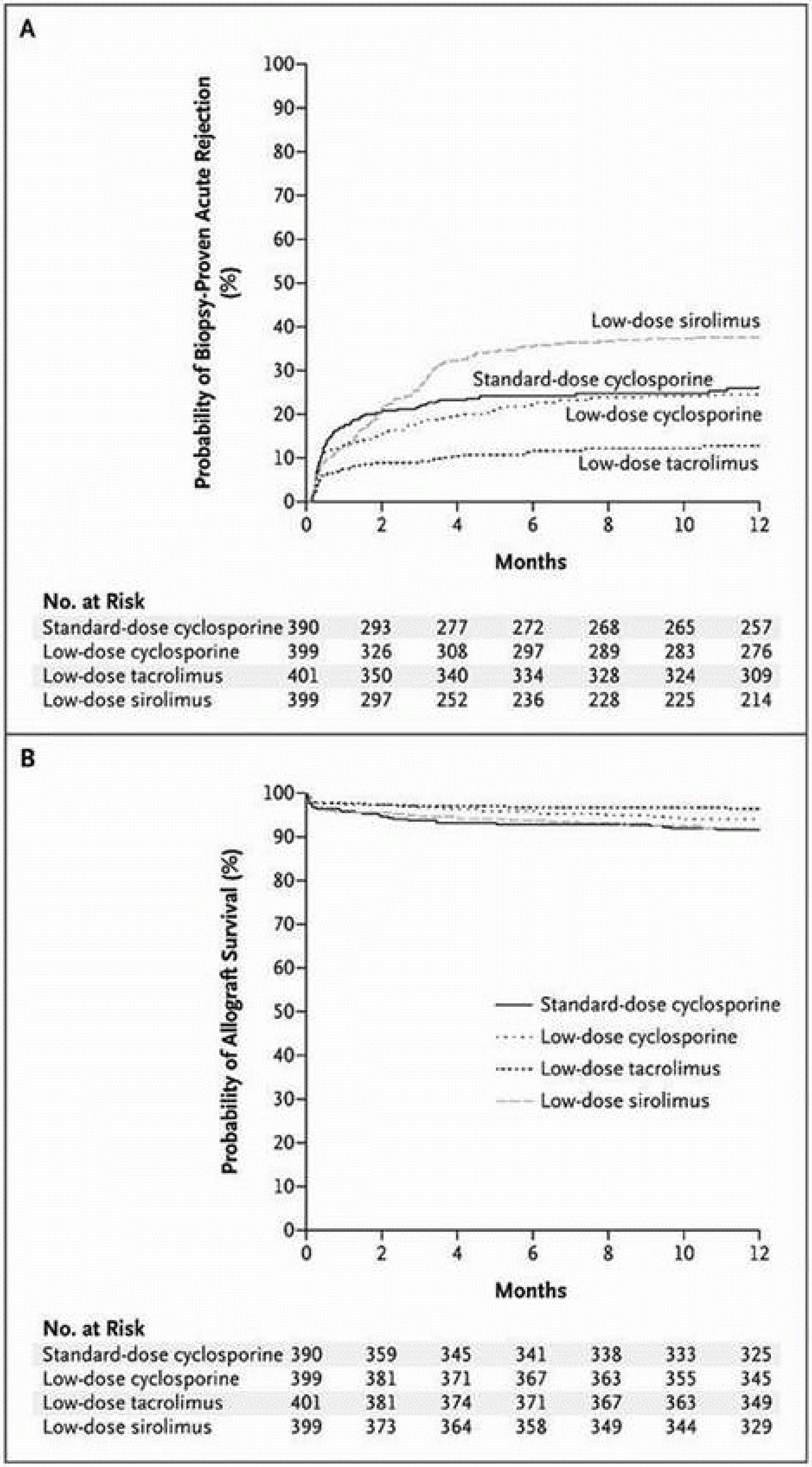


FIGURE 5.6 Cumulative probability of biopsy-proven acute rejection (**A**) and allograft survival (**B**), according to Study Group in the ELITE-Symphony trial. (From Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007;357:2562-2575, with permission.)

Both these studies provide support for the most commonly administered clinical protocol that consists of a low-dose calcineurin inhibitor (tacrolimus more frequently than cyclosporine), MMF, antibody induction, and low-dose steroids.

PART V. TREATMENT OF KIDNEY TRANSPLANT REJECTION

ACUTE CELLULAR REJECTION

First Rejection

Pulse Steroids

High intravenous doses of steroids, typically referred to as "pulses," reverse about 75% of first acute rejections. There are numerous ways to pulse a patient, and there is no good evidence that the higher-dose pulses (500 to 1000 mg methylprednisolone for 3 days) are more effective than the lower-dose pulses (120 to 250 mg oral prednisone or methylprednisolone for 3 to 5 days). Most programs still prefer to use intravenous methylprednisolone, which is given over 30 to 60 minutes into a peripheral vein. Pulse therapy is suitable for outpatient use when clinically indicated. The dose of prednisone can be continued at its previous level when the pulse is completed, although some programs elect to *recycle* the prednisone dose after the pulse has been completed. High maintenance doses of prednisone are not indicated. It is wise to repeat antibiotic prophylaxis with Bactrim after a steroid pulse.

Antibody Treatment

Thymoglobulin has largely replaced OKT3. Both are highly effective therapy for the management of a first acute rejection, and about 90% of such rejections are reversed. Despite the greater effectiveness of these agents, most programs still prefer to use pulse steroids as their first-line acute rejection therapy because of their convenience, lesser risks for side effects, and lower costs. Thymoglobulin or OKT3 may be a better first-line option for particularly severe or vascular rejections (Banff grade IIB or greater; see Chapter 14). The anti-CD25 monoclonal antibodies are not designed to be used in the treatment of established acute rejection.

Recurrent and Refractory Rejections

Repeated courses of pulse steroids may be effective in reversing acute rejections, but it is probably not wise to administer more than two courses of pulse therapy before resorting to antibody treatment. Many programs use antibody treatment for all second rejections unless the rejection is clinically mild or separated from the first by at least several weeks. Antibody treatment is particularly valuable for rejection episodes that

are steroid resistant and may succeed in reversing a high percentage of such rejections.

Some programs commence antibody treatment if there is not an immediate response to pulse therapy, whereas others wait several days. If renal function is deteriorating rapidly in the face of pulse steroids, it is probably wise to start antibody treatment early. Switching from cyclosporine to tacrolimus, or adding MMF or sirolimus in patients who have not previously received it, may be indicated for recurrent rejections.

The term *refractory rejection* is not well defined. It usually refers to ongoing rejection despite treatment with pulse steroids and antibody. The management of these patients is problematic. Second courses of depletional antibodies can be given in selected patients, and long-term graft function can be achieved in 40% to 50% of such patients. When deciding whether to give a second course of an antibody preparation, the clinician should bear in mind the severity and potential reversibility of rejection on biopsy and the increased risk for infection and malignancy that ensues, particularly if two courses are given close together.

Late Rejections

The terms *early rejection* and *late rejection* are not well defined. The differentiation between early and late rejection is not just semantic; each may respond differently to therapy. For practical purposes, a late rejection is one that occurs more than 3 to 4 months after transplantation and may be a first, or more frequently, a recurrent rejection. Late rejections can also be divided into those that occur in the face of apparently adequate immunosuppression and those that occur as a result of inadequate immunosuppression, often in nonadherent patients. Late rejections are often a prelude to chronic rejection and accelerated graft loss, and the histologic findings are often mixed. The initial treatment of a late rejection is typically pulse steroids. There is evidence that late rejections associated with noncompliance are more likely to respond to therapy. Use of Thy-moglobulin for late steroid-resistant rejection has not been systematically studied, and careful clinical judgment must accompany the decision to prescribe it; this decision should be made by a transplantation program. It may be wiser to accept graft dysfunction or loss rather than use repeated courses of high-dose immunosuppression in an already chronically immunosuppressed patient.

ANTIBODY-MEDIATED REJECTION

The clinical and pathologic recognition of antibody-mediated rejection are discussed in Chapters 9 and 14, with particular emphasis on the role of the C4D immunostain. Two related treatment protocols are effective: high-dose IVIG or low-dose CMVIG combined with plasmapheresis. A dose of 2 g/kg of IVIG is usually adequate; plasmapheresis plus CMVIG is usually performed every other day until levels of donor-specific antibodies are brought under control. In severe cases, for patients with high-titer donor-specific

antibodies, rituximab may reduce antibody burden and graft injury. Antibody-mediated rejection may recur and may be followed by episodes of acute cellular rejection. Patients must be monitored carefully in the weeks following treatment.

Episodes of antibody-mediated rejection may occur months, years, or even decades after transplantation likely because of the unrecognized persistence of donor-specific antibodies. Treatment of these late episodes is problematic because of the concomitant presence of other forms of allograft injury. The therapeutic options are the same as for the treatment of early episodes. Intensification of maintenance immunosuppression may be indicated but must be applied with great care.

IMMUNOSUPPRESSIVE MANAGEMENT OF CHRONIC ALLOGRAFT FAILURE

The clinical course, pathology, and multifactorial etiology of chronic allograft failure are discussed in Chapters 10 and 14. Before making changes in the immunosuppressive protocol in a patient with a failing allograft, every effort must be made to rule out potentially reversible causes of graft dysfunction, and it must be appreciated that many of the histologic changes are irreversible. Table 5.9 lists the issues that must be considered in all patients with presumed chronic allograft failure before changes are made in the immunosuppressive protocol.

TABLE 5.9 Steps to Take Before Manipulating Immunosuppression for Patients with Chronic Allograft Failure

1. Have reversible causes of deteriorating graft function been ruled out?
2. Is the patient clinically euvolemic?
3. Is there evidence of recurrent disease?
4. Have drug formulations been recently changed?

5. Have interfering drugs been introduced?

6. Is the patient (and physician!) adherent to the immunosuppressive regimen?

7. Have "nonimmune" interventions been applied?

Several single-center studies and retrospective analyses have suggested calcineurin inhibitor dose reduction or discontinuation while maintaining adjunctive therapy is a safe and effective means of delaying the inevitable progression of chronic allograft failure. The aptly termed Creeping Creatinine study (see Dudley and colleagues in "Selected Readings") was a multicenter, randomized, prospective study that evaluated the benefit of substitution of MMF for cyclosporine in patients with chronic allograft failure. An effective response to treatment was defined as a stabilization or reduction in the serum creatinine level, as evidenced by a flattening or positive slope of the 1/creatinine plot and no graft loss. The response rate was nearly 60% in the group whose cyclosporine was replaced by MMF, compared with 32% in the group whose cyclosporine dose was continued unchanged. This study and others support the following general principles that serve to guide immunosuppressive management of chronic allograft failure:

1. Intensification of calcineurin inhibitor dosage is generally not beneficial and may lead to exaggeration of nephrotoxicity.

2. Consideration should be given to reduction or even discontinuation of calcineurin inhibitor therapy. Such a therapeutic maneuver requires careful follow-up to screen for episodes of deteriorating graft function.

3. Reduction of calcineurin inhibitor dosage is generally accompanied by addition of, or continuation of, a non-nephrotoxic immunosuppressant.

4. There is most experience and documented benefit with MMF in these circumstances, although sirolimus may be an appropriate alternative in the absence of proteinuria.

5. Patients with chronic allograft failure that have deposition of C4D as a marker of ongoing humoral injury may represent a separate category that may benefit from intensification of immunosuppression or use of IVIG.

6. Introduction of a new immunosuppressive agent in previously immunosuppressed patients has potentially dangerous consequences. Patients should be monitored

carefully and consideration given to prophylaxis to prevent development of infectious complications.

7. High baseline doses of corticosteroids are not indicated. Pulse steroid therapy may be valuable for episodes of deteriorating function, but repeated treatment should be avoided. Ideally, use of pulse steroids in these circumstances should follow histologic confirmation of an element of acute rejection.

8. Because repeated pulse steroid therapy should be avoided, it is rarely indicated to perform repeated biopsies in patients with established chronic allograft nephropathy.

9. If graft function continues to deteriorate despite the above measures, plans should be made to prepare for end-stage renal disease treatment options, and immunosuppression should be withdrawn in a stepwise fashion when dialysis commences.

Selected Readings

Part I

Alloway RR, Isaacs R, Lake K, et al. Report of the American Society of Transplantation conference on immunosuppressive drugs and the use of generic immunosuppressants. Am J Transplant 2003;3:1211-1215.

Danovitch G. Mycophenolate mofetil: a decade of clinical experience. Transplantation 2005;80:S272-S274

Johnson O, Rose C, Webster A, et al. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. J Am Soc Nephrol 2008;19:1411-1418.

Kasiske B, Snyder J, Gilbertson D, et al. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant 2003;3:178-185.

Knight S, Russell N, Barcena L, et al. Mycophenolate mofetil decreases acute rejection and may improve graft survival in renal transplant recipients when compared with azathioprine: a systematic review. Transplantation 2009;87:785-794.

Letavernier E, Bruneval P, Vandermeersch S, et al. Sirolimus interacts with pathways essential for podocyte integrity. Nephrol Dial Transplant 2009;24:630-638.

Monaco A. The role of mTOR inhibitors in the management of posttransplant

malignancy. Transplantation 2009;87:157-163.

Naesens M, Kuypers, D, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol 2009;4:481-508.

Pham PT, Danovitch GM, Wilkinson AW, et al. Inhibitors of ADAMTS13: a potential factor in the cause of thrombotic microangiopathy in a renal allograft recipient. Transplantation 2002;74:1077-1081.

Pham PT, Pham PC, Danovitch G, et al. Sirolimus-associated pulmonary toxicity. Transplantation 2004;77:1215-1220.

Shaw L, Figurski M, Milone M, et al. Therapeutic drug monitoring of mycophenolic acid. Clin J Am Soc Nephrol 2007;2;1062-1072.

Sommerer C, Giese T, Meuer S, et al. Pharmacodynamic monitoring of calcineurin inhibitor therapy: Is there a clinical benefit? Nephrol Dial Transplant 2009;24:21-27.

Vincenti F, Friman S, Scheuermann E. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant 2007;7:1506-1514.

Weaver T, Kirk A. Alemtuzumab. Transplantation 2007;84 1545-1547.

Part II

Bollée B, Anglicheau D, Loupy A, et al. High-dosage intravenous immunoglobulin-associated macrovacuoles are associated with chronic tubulointerstitial lesion worsening in renal transplant recipients. Clin J Am Soc Nephrol 2008;3:1461-1468.

Brennan DC. Faith supported by reason: mechanistic support for the use of polyclonal antibodies in transplantation. Transplantation 2003;75:577-582.

Cantarovich M, Durrbach A, Hiesse C, et al. 20-Year follow-up results of a randomized controlled trial comparing antilymphocyte globulin induction to no induction in renal transplant patients. Transplantation 2008;86:1732-1737.

Lopez M, Clarkson M, Albin M, et al. A novel mechanism for anti-thymocyte globulin: induction of CD4+CD25+Foxp3+ regulatory cells. J Am Soc Nephrol 2006;17:2844-2853.

Vo A, Cam V, Toyoda M, et al. Safety and adverse events profiles of intravenous gammaglobulin products used for immunomodulation: a single-center experience. Clin J Am Soc Nephrol 2006;1:844-855.

Vo A, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med 2008;359:242-251.

Webster AC, Playford EG, Higgins G, et al. Interleukin 2 receptor antagonist for renal transplant recipients: a meta-analysis of randomized trials. Transplantation 2004;77:166-176.

Part III

Everly M, Everly J, Susskind B, et al. Bortezomib provides effective therapy for antibodyand cell-mediated acute rejection. Transplantation 2008:86:1754-1758.

Heeger P. Frontiers in nephrology: tolerance. J Am Soc Nephrol 2007;18:2240-2241.

Kasiske BL. Endpoint or turning point. Am J Transplant 2003;3:1463-1464.

Kawai T, Cosimi A, Spitzer T, et al. HLA-mismatched renal transplantation without maintenance immunosuppression. N Engl J Med 2008;358-353-361.

Lachenbruch P, Rosenberg A, Bonvini E, et al. Biomarkers and surrogate end-points in renal transplantation: present status and considerations in clinical trial design. Am J Transplant 2004;4:451-457.

Starzl T. Immunosuppressive therapy and tolerance of organ allografts. N Engl J Med 2008;358:407-411.

Van Gurp E, Schoordijk-Verschoor W, Klepper M, et al. The effect of the JAK inhibitor CP-690,550 on peripheral immune parameters in stable kidney allograft patients. Transplantation 2009;87:79-86.

Vincenti F, Kirk A. What's next in the pipeline? Am J Transplant 2008;8:1972-1981.

Yilmaz S, Tomlanovich S, Mathew T, et al. Protocol core needle biopsy and histologic chronic allograft damage index (CADI) as surrogate end point for long-

term graft survival in multicenter studies. J Am Soc Nephrol 2003;14:773-777.

Parts IV and V

Abramowicz D, Hadaya K, Hazzan M, et al. Conversion to sirolimus for chronic renal allograft dysfunction: risk factors for graft loss and severe side effects. Nephrol Dial Transplant 2008;23:3727-3729.

Arnol M, De Mattos A, Chung J, et al. Late steroid withdrawal and cardiovascular events in kidney transplant recipients. Transplantation 2008;86:1844-1848.

Augustinne J, Hricik D. Steroid withdrawal: Moving on to the next question. Am J Transplant 2009;9:3-4.

Craig J, Webster A, McDonald S. the case of azathioprine versus mycophenolate: do different drugs really cause different transplant outcomes? Transplantation 2009;87:803-804.

Danovitch GM. Immunosuppressive medications for renal transplantation: a multiple choice question. Kidney Int 2001;59:388.

Danovitch GM. Management of immunosuppression in patients with chronic allograft nephropathy. Kidney Int 2002;61:S80.

Dudley C, Pohanka E, Riad H, et al. Mycophenolate mofetil substitution for cyclosporine a in renal transplant recipients with chronic progressive allograft dysfunction: the Creeping Creatinine Study. Transplantation 2005;79:466-475.

Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007;357:2562-2575.

Gill JS, Tonelli M, Mix C, et al. The effect of maintenance immunosuppression medications on the change in kidney allograft function. Kidney Int 2004;65:692.

Halloran P, Bromberg J, Kaplan B, et al. Tolerance versus immunosuppression: A perspective. Am J Transplant 2008;8:1365-1366.

Hanvesakul R, Kubal C, Jham S, et al. Increased incidence of infections following the late introduction of mycophenolate mofetil in renal transplant recipients. Nephrol Dial Transplant 2008;23:4049-4053.

Krämer B, Del Castillo D, Margreiter L, et al. Efficacy and safety of tacrolimus compared with ciclosporin A in renal transplantation: three-year observational results. Nephrol Dial Transplant 2008;23:2386-2392.

Leichtman A. Balancing efficacy and toxicity in kidney transplant immunosuppression. N Engl J Med 2007;357:2625-2627.

Matas A. Resolved: in minimizing kidney transplant immunosuppression, steroids should go before calcineurin inhibitors. J Am Soc Nephrol 2007;18:3026-3030.

Schena F, Pascoe M, Albaru J, et al. conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT Trial. Transplantation 2009;87:233-242.

Vincenti F, Schena F, Paraskevas S, et al. for the FREEDOM Study Group. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. Am J Transplant 2008;8:307-316.

Walker J, Alloway R, Roy-Chaudhury P. A prospective trial of a steroid-free/calcineurin inhibitor minimization regimen in human leukocyte antigen (HLA)-identical live donor renal transplantation. Transplantation 2009;87:408-414.

Editors: **Danovitch, Gabriel M.**
Title: ***Handbook of Kidney Transplantation*, *5th Edition***

6

Living Donor Kidney Transplantation

Thu Pham

John Leppert

Peter Schulam

Advances in immunosuppressive therapy, refinement in surgical techniques, in public awareness, altruism, and goodwill, have allowed living donor kidney transplantation to evolve from the first successful identical twin donor transplantation in 1954 to the current practice whereby virtually all biologically related and unrelated, medically and psychosocially suitable individuals can be considered as donors. During the decade from 1996 to 2006, the number of living donor kidney transplantations in the United States almost doubled to more than 6000 per year but has since fallen somewhat. The increased rates of living donation have been attributed to the superior patient and graft survival rates achieved with living compared with deceased donor transplantation, the advent of laparoscopic donor nephrectomy, improved patient and public awareness, and as a response to the long waiting lists for a deceased donor transplant.

Both within the United States and around the world, there are wide variations in the use of living and deceased kidney donors These differences reflect varying medical and societal cultural values and varying realities in the availability of sophisticated care for patients with advanced kidney disease (see Chapter 1). Differences can also be driven by the availability of deceased donor organs relative to the number of patients waiting for transplants, attitudes of local physicians regarding the risk of living donation, and the degree of government oversight. In Spain, for example, where a highly effective mechanism for identifying deceased donors has helped keep waiting lists short, living donation accounts for less than 5% of all transplants. In many European countries, living donation accounts for less than 10% of transplants, although in the United Kingdom, there has been a steady increase in living donation that accounted for close to 40% of all kidney transplants in 2008. In Japan, strong cultural and, until recently, legal barriers have limited deceased donor transplants, and living donation is the most common form of transplantation. Although illegal throughout the developed world (see Chapter 18) and proscribed by national and international professional transplantation organizations, commercial living donation, typically from vulnerable populations,

remains a common practice in parts of the world. The World Health Organization has estimated that up to 10% of organ transplantations are performed in this manner. The Declaration of Istanbul on Organ Trafficking and Transplant Tourism (see Chapter 18 and Appendix) is designed to put an end to exploitation of living donors while promoting healthy and robust transplantation practice.

Part I of this chapter provides medical guidelines for evaluating a potential living donor candidate; part II reviews the relevant surgical issues and techniques; and part III discusses innovative and controversial aspects of living donation. Readers are referred to excellent resource material available on this topic, in particular the proceedings of the Amsterdam Conference on the Care of the Living Kidney Donor and the reviews authored by Davis and by Davis and Delmonico (see "Selected Readings").

PART I. EVALUATION OF LIVING KIDNEY DONORS

INFORMED CONSENT

Informed consent is a core value in living kidney donation (Table 6.1). Living donor consent is also discussed in Chapter 17. Emphasis on the adequacy of the consent process is particularly important because, as opposed to standard medical procedures, living donation is not specifically designed to help the donor or advance the donor's health. Moreover, living donation has the potential for contravening that basic tenet of medical ethics, *primum non nocere*. The person who gives consent to donate an organ must be a competent adult (possessing decision-making capacity); willing to donate; free from coercion; medically and psy-chosocially suitable; fully informed of the risks and benefits of donation; and fully informed of alternative treatments available to the recipient (i.e., to understand that in the absence of their donation, the patient can, in most circumstances, continue dialysis). Two other principles of living donor consent have been endorsed: that of *equipoise*—the benefits to both the donor and recipient must outweigh the risks associated with the donation and the transplantation of the live donor organ; and that it is clear to the potential donor that his or her participation is completely voluntary and may be withdrawn at any time. To ensure that these principles are applied, it has been recommended that programs performing living donor transplantations have an independent donor advocate who is not part of the team caring for the recipient. The availability of such an advocate (who may be the evaluating physician as long as he or she is not responsible for the care of the recipient) is now mandated in the United States.

A separate consent should be obtained for the donor evaluation. This helps ensure that, in addition to being informed of the risks of donation, the

---

donor is informed about all aspects of organ donation and the implications of the evaluation process (Table 6.2).

TABLE 6.1 Suggested Elements for Consent in the Living Donor Evaluation Process

The potential donor should understand the following:

- Undergoing evaluation is not a commitment to donate.
- I can stop at any time.
- The physicians may turn me down as a donor, and will inform me why.
- I will be evaluated by an independent donor evaluation doctor or team to protect my interests.
- The information obtained during the course of the evaluation is confidential.
- I will be tested for AIDS, hepatitis, and other infectious diseases.
- I may get unexpected information during the evaluation process that may have implications for my future health and insurability.
- There may be risks and discomfort associated with some of the testing (e.g., blood draws, intravenous contrast).

- There are potential financial costs to me related to time off work, travel expenses, and the like that might not be reimbursed.
- There are potential study uses to the information obtained during the evaluation. I may be asked to participate in a living donor registry.
- It may be suggested to me that I have routine long-term medical follow-up after kidney donation.
- There are alternative treatments available to the recipient other than my donating a kidney to him or her.

Modified from a personal communication from D. Cohen, M.D.

TABLE 6.2 Consent for Medical Evaluation

The potential donor should be informed that he or she must undergo the following:

- A complete history and physical examination
- General laboratory testing

- Screening for HIV, hepatitis, and other infectious diseases
- Imaging studies requiring the use of intravenous contrast The potential donor should understand the following:
  - I may get unexpected information during the evaluation process that may have implications for my future health and insurability.
  - There may be risks and discomfort associated with some of the testing (e.g., blood drawn, intravenous contrast).
  - There may be potential short- and long-term risks associated with the surgical procedure.
  - I may need routine long-term follow-up after kidney donation.
  - The benefits to both the donor and recipient must outweigh the risks associated with the donation and the transplantation of the live organ.

THE EVALUATION PROCESS

The major components of the evaluation of potential living kidney donors are shown in Figure 6.1.

Psychosocial Evaluation

The psychosocial evaluation is an important initial step in the evaluation of the potential donor (see also Chapters 17 and 20). It also presents a valuable forum for fulfilling the tenets of informed consent, exploring donor motivation, and excluding coercion. Significant psychiatric problems that would impair the person's ability to give informed consent or that might be negatively affected by the stress of surgery are considered contraindications to living donation (see Chapter 17, Table 17.4). The social support of the potential donor should be deemed adequate. The psychosocial evaluation of so-called nondirected or altruistic donors (see below) and donors who do not have a significant personal relationship with the recipient is particularly important because these donors may not enjoy the psychological gain of seeing the recipient benefit from their altruism (see Chapter 17, Table 17.1). Most donors can look forward to stable or improved sense of psychological well-being and can be told of such.

The psychosocial evaluation must consider the possibility of economic or other forms of coercion. The principles by which donors can be reimbursed for legitimate expenses incurred as a result of the donation or preparation for donation are addressed in the Declaration of Istanbul (see Appendix) and in the National Organ Transplant Act (see Chapter 18). In the United States, all medical costs directly associated with donation are covered by the health insurance of the recipient. The federal government and other employers provide for salary benefits for a 1-month period after donation, some states offer limited tax deductions for donation-related expenses, and a National Living Donor Assistance Center provides reimbursement of legitimate out-of-pocket expenses for donors who can document financial need. There is no mechanism however, for routine reimbursement of out-of-pocket expenses.

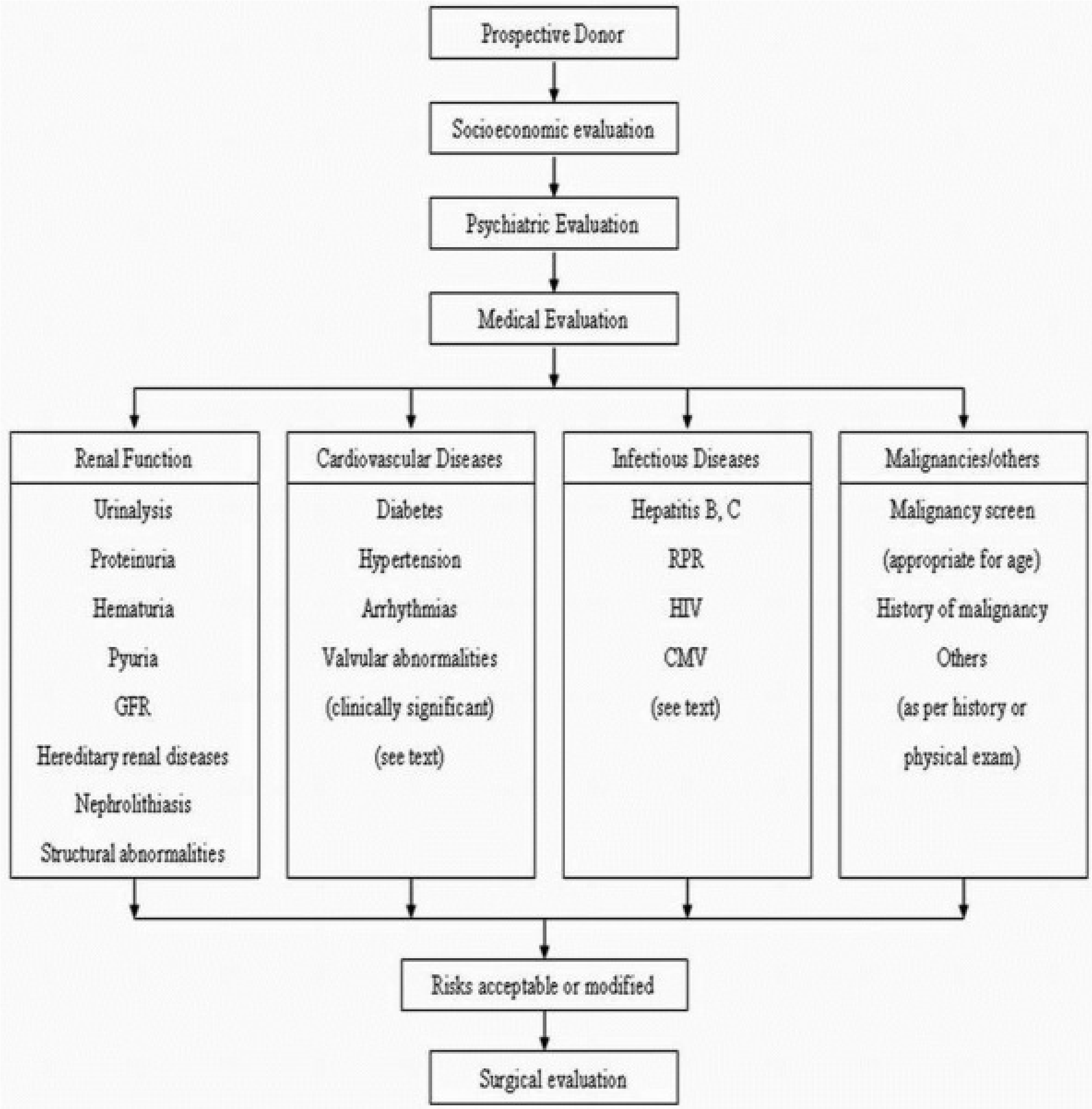


FIGURE 6.1 Major components of the evaluation of potential living kidney donors.

Medical Evaluation

Preliminary Laboratory Evaluation: Donor Typing to Determine the Risk for Acute Transplant Failure

Mandatory preliminary laboratory evaluation of a potential living donor includes determination of ABO blood group compatibility, crossmatching against the potential recipient, and HLA tissue typing. Because of the high costs of HLA laboratory testing and the availability of effective immunosuppressive therapy that minimizes the clinical significance of differences of HLA matching of living donors, some centers elect to perform HLA typing only in sensitized transplant candidates.

Which Donor to Choose?

In cases in which more than one donor is available, selection of the most appropriate donor depends on the degree of HLA matching and donor age. Biologically related donors are generally preferred over unrelated donors. When more than one family member is available, it is logical to commence evaluation of the

best matched relative (i.e., a two-haplotype match versus a one-haplotype match). If the donors have similar match grade (i.e., a one-haplotype-matched parent and a one-haplotype-matched sibling), it may be advisable to choose the older donor with the thought that the younger donor would still be available for donation if the first kidney eventually fails. When more than one one-haplotype-matched sibling is available, it may be worthwhile to check the tissue typing of one parent to determine which siblings shares the noninherited maternal antigens (see Chapter 3). Such sharing may improve long-term graft survival.

It is often a good prognostic sign when the donor attends the recipient's pretransplantation evaluation appointments. The initial approach to the potential donor should ideally come from the patient and not the patient's nephrolo-gist, transplant physician, or surgeon. In cases in which patients hesitate to approach family members, the nephrologist and transplant team should be prepared to facilitate the discussion of donation. Written material explaining the donation process can often help to alleviate the fears and anxiety of potential donors. Excellent educational material is available on the websites of major nephrology and transplant-related organizations. Educational material that is home-based and culturally sensitive may be particularly effective.

Parents often are reluctant to turn to their children as potential donors, yet as those parents age, it becomes less and less likely that a donor from their own generation will be available. It is useful to point out to parents that their grown children are adults who are capable of making independent decisions; that the welfare of the donor will be protected in the evaluation and donation period; and that, if they exclude their children as donors, they may be preventing them from enjoying the psychological gain of helping a beloved parent. Older patients will often insist they would have been prepared to donate to their own parents while simultaneously expressing reluctance to permit their own children to donate to them.

Donor Age

Advanced age can increase the risk for perioperative complications, but there is no mandated upper age limit for living kidney donation. About 25% of programs in the United States exclude donors older than 65 years, and although many programs specify no upper age limit, donation after the age of 70 years is relatively uncommon. There is a trend toward using older donors, and the outcome of these donations, particularly to

older recipients, is reported to be excellent.

With respect to younger donor age, most programs regard 18 years to be a firm lower age limit. Donors in their late teens and early 20s must be carefully evaluated for the maturity of their understanding of the donation process and to ensure they are not being subjected to overt or covert pressure. Their long life span and hence exposure to the risk for renal disease must be considered, particularly when there is a potential element of heredity in the etiology of the recipient's renal disease.

Challenges in the Counseling of Older Transplant Recipients

Nearly 10% of all living donations are to recipients who are older than 65 years. Transplantation of living donor kidneys into recipients older than 70 years of age can be practically and ethically challenging. The elderly transplant candidates may be faced with a difficult dilemma: to wait for many years for a deceased donor kidney with the knowledge that their medical condition may continue to deteriorate, or to resort to a young family member for kidney donation while they are still medically suitable for the surgery and young and robust enough to enjoy the transplant.

When the potential donor is considerably younger than the recipient, the following questions should also be addressed: Is it reasonable to transplant a kidney from a very young donor into an elderly recipient who will only benefit from the kidney for a very limited number of years? Should the anticipated extra years of life gained by the recipient place any limitations to the living donor transplantation? There are no formal guidelines that address the acceptable age disparity between living donors and recipients. In most cases, it is best to leave the decision in the hands of an educated and informed potential donor.

Nonetheless, when an elderly transplant candidate does consider a living donor transplant, it is advisable that the transplant be performed as early as possible to maximize the benefit of the procedure. Furthermore, transplantation within a timely period has been shown to increase overall life expectancy, quality-adjusted life expectancy, and comorbidities for transplant recipients of all ages, whereas prolonged waiting time greatly decreased the clinical and economical benefit of transplantation.

General Assessment

The universal medical goals in the kidney donation evaluation process are to ensure that the potential donor has the following characteristics:

- Is sufficiently healthy to undergo the surgical procedure
- Has normal kidney function with minimal future risk for kidney disease
- Represents no risk to the recipient in terms of communicable disease or malignancy

transmission

- Is not at increased risk for medical conditions that might require treatments that could endanger his or her residual renal function

History, Physical Examination, Laboratory Testing, and Imaging

Living donor evaluation requires a thorough history and physical examination supplemented by laboratory testing, age-appropriate medical screening, and renal imaging (Table 6.3). Donor history or characteristics known to confer significant risk to either the donor or recipient can automatically preclude donation. Obvious contraindications should be determined at the beginning of the donor assessment before subjecting unqualified donors to unnecessary tests (Table 6.4). Female patients should not be evaluated while pregnant or planning to become pregnant in the immediate future. The appropriate postpartum time when donor evaluation may be resumed has not been determined, but if the donor so desires, it is reasonable to evaluate for donation 6 months postpartum. Desire for future pregnancy does not contraindicate donation. Unilateral donor nephrectomy does not increase obstetrical risks or complications.

EVALUATION OF FUTURE DONOR RISK

The systematic evaluation of future donor risk focuses on renal function and covert renal disease; cardiovascular disease risk factors include hypertension, diabetes, and obesity; risk for communicable disease or malignancy transmission to the recipient; and assessment of surgical risks.

Assessment of Renal Function and Covert Renal Disease

Glomerular Filtration Rate

Measurement of creatinine clearance based on a 24-hour urine collection is generally adequate to assess the donor's renal function, although some centers prefer iothalamate or diethylenetriamine pentaacetic acid (DTPA) clearance. Many centers start with a 24-hour urine collection for creatinine clearance and

---

only proceed to a renal nuclear scan study in cases with borderline renal function. It must be noted, however, that elderly donors, donors with low muscle mass, and vegetarians may have a low creatinine clearance without intrinsic renal disease. Creatinine-based prediction equations are not reliable in the donor population with relatively normal renal function and should not be used as the sole estimate of glomerular filtration rate (GFR). A 24-hour urine collection is the preferred method to

assess renal function because it also offers accurate data for proteinuria.

TABLE 6.3 Living Donor Medical Evaluation

Laboratory Tests
• Blood group, HLA typing, crossmatch
• Urinalysis and urine culture
• Twenty-four-hour urine collection for protein and creatinine clearance or glomerular filtration rate determination by nuclear medicine test
• Complete blood count, prothrombin time, partial thromboplastin time
• Comprehensive metabolic panel (electrolytes, transaminase levels, albumin, bilirubin, calcium, phosphorus, alkaline phosphatase)
• Viral serologies: HIV, hepatitis B and C viruses, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, RPR
• Prostate-specific antigen in men 50 years and older (in African American men older than 40 years and in those with two or more first-degree relatives with prostate cancer)

- Human chorionic gonadotropin quantitative pregnancy test in women younger than 55 years
- Serum protein electrophoresis in prospective donors older than 60 years

Other Tests

- Electrocardiogram
- Chest radiograph
- Papanicolaou test (for women)
- Mammogram for women 40 years and older
- Renal imaging: spiral computed tomography (CT), CT angiogram, or magnetic resonance angiogram

Further Testing Depending on Age, History, Abnormal Laboratory Findings, and Family History Screening

- Colonoscopy if 50 years or older

- Cardiac screening: echocardiograph, nuclear medicine stress test Twenty-four-hour ambulatory blood pressure monitoring
- Renal biopsy
- Cystoscopy
- PPD skin test
- Screening for hypercoagulability
- Glucose tolerance test with family history of diabetes mellitus or risk factors for development of diabetes (see text)

Although there is no absolute consensus on the level of renal function below which a person would not be deemed an acceptable donor, most centers use a cutoff GFR of 80 mL/min/1.73 m^2. Considerations for the lower limit of

renal function allowable for kidney donation include a predicted fall in GFR to 75% of predonation level and the normal decline in GFR with aging at a rate 4 to 5 mL/min/1.73 m^2 per decade of life starting at age 20 years. Other criteria used to preclude kidney donation include a projected GFR with removal of one kidney at 80 years of less than 40 mL/min/1.73 m^2. Healthy vegetarians tend to have a lower GFR than meat-eaters.

TABLE 6.4 Contraindications to Living Kidney Donation*

Absolute Contraindications

- Evidence of renal disease (glomerular filtration rate < 80 mL/min, microalbuminuria or overt proteinuria)
- Significant renal or urologic abnormalities
- Transmissible infectious disease (HIV infection, hepatitis B, hepatitis C)
- Active malignancy
- Chronic illness that places patient at significant risk to undergo surgery
- Poorly controlled psychiatric illness or active substance use
- Cognitive deficit
- Current pregnancy
- Hypertension, uncontrolled or requiring multiple medications

- Diabetes mellitus
- Recurrent nephrolithiasis or bilateral stones
- History of thrombotic disorders with risk factors for future events or inherited hyper-coagulable states[†]

Relative Contraindications

- Age < 18 or > 65 years
- Borderline or mild hypertension (see text)
- Borderline urinary abnormalities in the absence of renal function impairment
- Single prior episode of nephrolithiasis without evidence of secondary risk
- Obesity
- Young donor with risk factors for future development of diabetes mellitus (see text)

◗	Jehovah's Witness patient

*Criteria may differ among transplantation centers.

† For example, the presence of lupus anticoagulant or anticardiolipin antibody, Factor V Leiden, or prothrombin gene mutation (FII-20210).

Abnormal Urinalysis Results

Proteinuria. Proteinuria greater than 250 mg per day, in general, is a sign of renal disease and precludes donation. The collection should be repeated and its accuracy checked when the result is abnormal. An overestimate of proteinuria should be suspected if total urine creatinine-to-body weight ratios are greater than 25 mg/kg (>20 μmol/kg), especially in those with low muscle mass. An underestimate of proteinuria may have occurred if the total urine creatinine-to-body weight ratios are less than 15 mg/kg (<132 μmol/kg). In those with borderline high proteinuria, it is especially important to rule out undercollections. Spot protein-to-creatinine ratios are not recommended because minimal yet clinically significant proteinuria may be missed.

Transient causes of proteinuria, including fever, urinary tract infection, or intense exercise, should be excluded. Orthostatic proteinuria, defined as elevated urine protein with assumption of the upright posture and normal protein excretion during recumbency should be ruled out. This benign phenomenon usually occurs in younger age groups and does not necessarily preclude donation. Borderline high proteinuria can be further evaluated for microalbuminuria, a more reliable marker of intrinsic renal disease. The presence of microalbuminuria in such cases should preclude kidney donation.

Hematuria. Isolated hematuria, defined as greater than five red cells per high-power field, can occur with intrinsic renal diseases or abnormalities within the urinary tract. In premenopausal women, contamination from menstruation should be ruled out. The concurrent presence of urinary casts or dysmorphic red blood cells with or without proteinuria is indicative of underlying intrinsic renal disease. A family history of renal disease, urinary tract infections, stones, and tumors should also be excluded. Donor candidates with persistent isolated microscopic hematuria may require a complete urologic evaluation. A cystoscopy to exclude bladder pathology may be necessary. In the absence of any specific abnormalities, a kidney biopsy may be indicated to rule out

glomerular pathology such as Alport syndrome, thin basement membrane disease, and immunoglobulin A (IgA) nephropathy. The risks intrinsic in renal biopsies must be considered in the overall risk for donation. If a full evaluation for persistent isolated microscopic hematuria is negative, further evaluation for donation may be resumed because the risk for progressive renal disease is very small.

Pyuria. Common causes of pyuria such as urinary tract infections and prostatitis should be ruled out. In the face of persistent pyuria, renal tuberculosis should be ruled out with three morning urine acid-fast bacilli cultures. If no obvious infectious or inflammatory source can be found, a renal biopsy should be considered to rule out interstitial nephritis or chronic pyelonephritis. Evidence for renal tuberculosis, interstitial nephritis, or pyelonephritis is a contraindication to donation.

Inherited Renal Disease

The medical evaluation should specifically probe for possible familial or hereditary renal disease, particularly when evaluating prospective living related donors. Knowledge of the recipient's renal disease is a critical part of donor evaluation. For some hereditary renal diseases, a clear family history or unequivocal biopsy findings can provide valuable information; for others, in which biopsy documentation of the recipient's underlying renal disease is lacking, family information regarding extrarenal manifestations, such as ocular and hearing abnormalities in Alport syndrome, may provide information invaluable to the decision-making process of kidney donation.

Autosomal Dominant Polycystic Kidney Disease. The most commonly encountered hereditary renal disease is autosomal dominant polycystic kidney disease (ADPKD). The diagnosis of ADPKD in a person at risk is defined by specific age-dependent criteria. For ADPKD1, the presence of one or more cysts per kidney, or two or more cysts in one kidney for those younger than 30 years; two or more cysts in each kidney for those age 30 to 59 years; and four or more cysts in each kidney for those 60 years of age or older. In contrast to ADPKD1, ADPKD2 may present later in life, and the use of ADPKD1 diagnostic criteria may lead to false-negative results. Unified critera for ultrasonographic diagnosis of ADPKD have been suggested for clinical circumstances where molecular genotyping is seldom performed (see Pei et al in Selected Readings).

For potential donors older than 30 years, it is safe to proceed with donor nephrectomy if ultrasound or computed tomography (CT) reveals no evidence of

cysts. Renal ultrasound is a sensitive, relatively inexpensive and noninvasive method of screening but can miss cysts smaller than 1 cm. For potential donors between the ages of 20 and 30 years, a negative ultrasound alone does not rule out ADPKD, and donation cannot be recommended without other evidence supporting the absence of the disease. It has been suggested that the greater sensitivity of heavily T2-weighted magnetic resonance imaging (MRI) in detecting smaller cysts may reliably exclude ADPKD at younger ages. However, the diagnostic criteria for ADPKD based on MRI have not been

established. Genetic studies, such as linkage analysis and direct DNA sequencing, are gold-standard diagnostic tests. These tests, however, are often not feasible, routinely available, or 100% sensitive. Linkage analysis is rarely performed because of the requirement for testing of multiple affected and unaffected family members. Direct DNA sequencing may yield a definitive result in only 70% of cases. Nonetheless, it is generally considered safe to proceed with kidney donation if both imaging studies and genetic testing exclude the presence of ADPKD. For more information on ADPKD testing, readers are referred to http://www.Athenadiagnostic.com.

Alport Syndrome. Most cases of Alport syndrome are transmitted as an X-linked recessive trait. In 15% of cases, the transmission is autosomal recessive. There are many different mutations that can lead to Alport syndrome, but they all cause a defect in the α_5 chain of type IV collagen in the basement membrane, which can lead to glomerulosclerosis and eventual renal failure. The mutation can be associated with basement membrane abnormalities in the eye and sensorineural part of the ear, causing ocular abnormalities such as lenticonus and deafness, respectively. Persons being evaluated as kidney donors with a family history of Alport syndrome need to be carefully screened for hematuria, hypertension, sensorineural hearing loss, and ocular abnormalities (anterior lenticonus, cataracts, retinal lesions). The absence of hematuria in an adult male 20 years of age or older essentially excludes the presence of the genetic defect. Adult female siblings with normal urinalysis have a low risk for being carriers and are acceptable as donors. However, female relatives with persistent hematuria are most likely carriers of the mutation and have a 10% to 15% risk for developing chronic kidney disease. Donation in the latter group is not advisable. Although genetic testing is possible, it is not readily available and generally not performed.

Thin Basement Membrane Disease. The biopsy diagnosis of thin basement membrane disease (TBMD) can follow an extensive evaluation for persistent or strong family history of microscopic hematuria. Although TBMD generally has a benign prognosis, the impact of hyperfiltration after uninephrectomy may increase the risk for renal dysfunction. Donation from individuals with TBMD remains controversial. Prospective donors with TBMD may still be considered if they are older than 40 years of age and IgA nephropathy or Alport syndrome have been excluded. Early biopsy findings of female carriers of X-linked Alport syndrome and TBMD, however, may be difficult to differentiate histologically. Clinical characteristics that help to distinguish TBMD from IgA nephropathy and Alport syndrome are shown in Table 6.5. The presence of hypertension, proteinuria, or both precludes donation. Prospective donors must be counseled that although TBMD typically has a benign outcome, slowly progressive renal insufficiency may occur. Potential donors should also be advised that long-term donor risk remains unknown and that any effect of TBMD on allograft function remains unclear.

Familial Primary Glomerulonephritis. Familial forms of glomerulonephritis should be considered when more than one family member is affected with renal disease.

Idiopathic steroid-resistant focal segmental glomerulosclerosis (FSGS), a form of glomerulopathy linked to mutations of various podocyte-associated proteins, is probably the best described familial primary glomerulonephritis. Other forms of familial glomerulonephritis such as IgA nephropathy, membranoproliferative glomerulonephritis, and familial membranous nephropathy have also been described. Genetic analysis for idiopathic steroid-resistant FSGS may be possible, but not readily available.

TABLE 6.5 Clinical Characteristics that Help Distinguish Thin Basement Membrane Disease from IgA Nephropathy and Alport Syndrome

Thin Basement Membrane Disease
• Gross hematuria uncommon
• Positive family history of hematuria
• Negative family history of renal failure
IgA Nephropathy
• Episodic gross hematuria common
• Family history of hematuria may occur in isolated cases

- May have family history of renal failure

Alport Syndrome

- May have episodic gross hematuria
- Typically with positive family history of renal failure
- Deafness may be present in families in which there is an X-linked mode of inheritance

Systemic Lupus Erythematosus. Systemic lupus erythematosus (SLE) occurs in about 12% or more of first-degree relatives. Prospective living related donors should be screened for antinuclear antibody (ANA), complement levels, and abnormal urinary findings. Antiphospholipid antibody should be performed at the discretion of the clinicians, as dictated by a history of deep vein thrombosis (DVT), stroke, pulmonary embolism, fetal loss, thrombocytopenia, hemolytic anemia, or livedo reticularis. Family member of a patient with SLE who has a positive ANA has an about 40-fold increased risk for developing lupus and generally should be excluded from donation.

Screening for Sickle Cell Trait. The literature on the potential risks to live kidney donors with sickle cell trait is sparse. Many programs do not routinely screen donors for sickle cell trait, but many do exclude donors with sickle cell trait when the diagnosis is made. There are currently no guidelines with respect to sickle trait screening, and center practice regarding exclusion of donors with sickle cell trait varies widely. Nonetheless, prospective donors with unexplained hematuria, women with recurrent bacteriuria or pyelonephritis, and those with a family history of sickle cell disease or sickle cell trait should be screened for sickle cell trait. It is probably prudent to exclude prospective donors with documented recurrent bacteriuria or pyelonephritis and those with evidence of papillary necrosis on imaging studies. Young prospective donors should be forewarned of the increased risk for medullary carcinoma, and regular postdonation follow-up is advised.

Nephrolithiasis

The routine evaluation of donors should identify the presence of kidney stones. The concern for kidney donation in a person with a prior history of kidney stones is the potential for disease recurrence in the remaining kidney with resultant obstructive uropathy and renal failure. However, prospective donors with a distant history of stones (>10 years) but without metabolic abnormalities associated with stone formation (e.g., hypercalcemia, hyperuricemia, hyperoxaluria, hypocitraturia, or metabolic acidosis) are at low risk for stone recurrence and may be acceptable as living donors. An asymptomatic potential donor with a current single stone may be suitable for donation if the current stone size is less than 1.5 cm or potentially removable during transplantation. In addition, further stone evaluation must reveal no evidence of metabolic abnormalities, urinary tract infection, or nephrocalcinosis.

Prospective donors with a history of kidney stone must be advised of increased risk for recurrence (50% in 5 to 7 years). The presence of underlying medical disorders associated with a high risk for recurrent stones such as cystinuria, primary or enteric hyperoxaluria, inflammatory bowel disease, and sarcoidosis contraindicates donation. A history of struvite stones contraindicates donation because these stones are associated with infection that are difficult to eradicate. A history of a single stone episode associated with treated primary hyperparathyroidism and normocalcemia does not necessarily preclude donation. The presence of nephrocalcinosis, bilateral stones, or history of stone recurrence despite preventive therapy contraindicates donation.

Spiral CT of the kidneys should be used to detect the current presence of stones or nephrocalcinosis in persons with a history of stone disease. Plain films cannot adequately assess radiolucent and small stones, whereas ultrasound can miss detection of the latter. Timed urine collections to assess metabolic abnormalities are not as predictive of the risk for recurrent stones as clinical parameters such as age and amount of time passed since an initial episode. Nevertheless, the data obtained may aid dietary counseling and selection of appropriate therapy. A stone initially detected in a person older than 50 years is unlikely to recur. In contrast, the risk for stone recurrence is higher in individuals aged 25 to 35 years and must be considered during the donor evaluation process.

Cardiovascular Disease Risk Assessment

An important goal in the donor evaluation process is to minimize health risks to the donors and to ensure adequate future long-term renal function. There is evidence suggesting that even moderate renal impairment is associated with an increased risk for cardiovascular disease, although it must be emphasized that this evidence comes from patients who have lost function because of disease. Studies following living kidney donors for 25 years or more have consistently demonstrated long-term safety following donor nephrectomy without significant increases in kidney disease, although there may be a trend for a small increase in systolic blood pressure.

Hypertension

In general, screening for hypertension in a potential donor includes blood pressure measurement on three separate occasions. Elevated blood pressure, as defined by the Joint National Committee (JNC 7) for the diagnosis of hypertension, requires further evaluation with ambulatory blood pressure monitoring (ABPM) to exclude white-coat hypertension. The donor should have a mean awake blood pressure less than 135/85 mm Hg and sleep blood pressure less than 120/75 mm Hg. Most transplantation centers exclude prospective donors

---

with blood pressures greater than 140/90 by ABPM from donation. An echocardiogram may be considered to evaluate for cardiac hypertrophy in cases with borderline high blood pressure, or abnormalities suggesting cardiomegaly or left ventricular hypertrophy on chest radiograph or electrocardiogram, respectively. A history of mild hypertension may be acceptable for donation if the prospective donor is not African American and is older than 50 years without evidence of microalbuminuria or end-organ damage. In these circumstances, the risk for hypertension-induced chronic kidney disease within the prospective donor's lifetime is very small. The prospective donor with mild hypertension must have normal GFR for age and blood pressure well controlled with lifestyle and behavioral modifications or use of no more than a single antihypertensive agent.

Diabetes

Diabetes mellitus is defined as having a fasting plasma glucose (FPG) level of at least 126 mg/dL (≥7.0 mmol/L), or a plasma glucose level of at least 200 mg/dL (11.1 mmol/L) 2 hours after 75-g oral glucose challenge (oral glucose tolerance test), confirmed by repeat testing on a different day. FPG values between 100 and 125 mg/dL (5.6 to 6.9 mmol/L) define impaired fasting glucose (IFG), and 2-hour plasma glucose values between 140 and 199 mg/dL (7.8mmol/L to 11.1 mmol/dL) define impaired glucose tolerance (IGT). The diabetes guidelines acknowledge that both IFG and IGT are important predictive factors for the progression to overt diabetes and well-established risk factors for microvascular and cardiovascular disease.

All potential living donors should have a fasting plasma glucose estimation to exclude undiagnosed diabetes or glucose intolerance. Prospective donors with a fasting blood sugar between 100 and 125 mg/dL and those with risk factors for the development of diabetes in the absence of abnormal fasting blood sugar should be evaluated with oral glucose tolerance test (OGTT). The latter include individuals with first-degree relative with type 2 diabetes, history of gestational diabetes or large birth weight (>9 pounds at delivery), obesity defined as having a body mass index (BMI) of more than 30, fasting hypertriglyceridemia of at least 250 mg/dL, high-density lipoprotein (HDL) level of no more than 35 mg/dL, or blood pressure higher than 140/90 mm Hg. Donors younger than

40 years with a second-degree relative with type 2 diabetes mellitus should also undergo OGTT.

Most transplantation centers regard established diabetes mellitus as a contraindication to living donation, and many centers exclude individuals deemed high risk. Absolute and relative contraindications to donation in the presence of glucose intolerance are shown in Table 6.6. Individuals with IFG and IGT should be counseled on lifestyle modifications, including weight control, diet, exercise, and tobacco avoidance. Prospective donors with IFG or IGT should be assessed on an individual basis. Donation is not recommended in individuals with mild or borderline IGT and additional risk factors. Individuals with blood glucose in the high range of IFG probably should not donate because of the greater tendency for deterioration. Prospective donors should be forewarned that both IFG and IGT are important predictive factors for progression to overt diabetes.

Women with a history of gestational diabetes have a high lifetime risk for developing type 2 diabetes—as high as 50% to 70% in some series—with the greatest increase in risk in the first 5 years after delivery, and a plateau in risk after 10 years. Therefore, acceptance for donation and counseling for future risk can be dictated by these time frames. An OGTT in conjunction with stimulated insulin levels may be more helpful in determining risk than an OGTT alone because some women with a history of gestational diabetes may have evidence of insulin resistance that may portend a higher risk for future development of overt diabetes.

TABLE 6.6 Absolute and Relative Contraindications to Donation in Prospective Donors with Impaired Glucose Tolerance

Absolute Contraindications
- Known diabetes mellitus
- Fasting plasma glucose (FPG) level ≥ 126 mg/dL (7.0 mmol/L) on two or more occasions

- Plasma glucose level > 200 mg/dL (11.1 mmol/L) 2 hours after 75 g oral glucose challenge (oral glucose tolerance test) on two or more occasions

Relative Contraindications

- Impaired fasting glucose (IFG), defined as FPG values between 110 and 125 mg/dL (6.1-6.9 mmol/L)
- Impaired glucose tolerance (IGT), defined as 2-hour plasma glucose values between 140 and 199 mg/dL (7.8 mmol/L to 11.1 mmol/dL)
- Individuals with IFG or IGT should be counseled on lifestyle modifications, including weight control, diet, exercise, and tobacco avoidance
- Prospective donors with IFG should be assessed on an individual basis
- Donation generally not recommended in:
- Individuals with mild or borderline IGT and additional risk factors (first-degree relatives of patients with type 2 diabetes mellitus, obesity, gestational diabetes mellitus, and dyslipidemia)
- Individuals with blood glucose in the high range of impaired glucose tolerance (110-125 mg/dL, 6.1-6.9 mmol/L) should probably not donate

because of the greater tendency for deterioration

- Prospective donors should be forewarned that both IFG and IGT are important predictive factors for the progression to overt diabetes.

Obesity

Obesity, defined as having a BMI greater than 30, is associated with increased risk for surgical complications as well as future medical problems including diabetes, hypertension, nephrolithiasis, glomerular disease with associated albuminuria or overt proteinuria, and end-stage renal disease (ESRD). Among obese individuals, an increased risk for proteinuria and renal insufficiency has been reported following unilateral nephrectomy. The relative risk for developing ESRD is threefold for a BMI between 30 and 35 and nearly fivefold for a BMI of 35 to 40. The impact of other medical issues that may be present in this group, such as cardiovascular disease, sleep apnea, or hepatosteatosis, should also be carefully assessed. Obese potential donors should be encouraged to lose weight before kidney donation. Donation is not advisable in the presence of other comorbid conditions. About 50% of transplantation programs in the United States regard a BMI greater than 35 as a contraindication to donation, and 10% report excluding donors with a BMI over 30.

RISK FOR COMMUNICABLE DISEASE OR MALIGNANCY TRANSMISSION TO THE RECIPIENT

The presence of chronic viral infections, such as HIV, hepatitis B, and hepatitis C, in the donor contraindicates donation because of the high risk for disease transmission to the recipient (see Chapter 11) and the risk for virus-induced renal disease in the donor. Transmission of human T-cell lymphotropic virus

(HTLV) and human herpesvirus-8 (HHV-8) to the recipient has been associated with the development of T-cell leukemia and spastic paraparesis, and Kaposi sarcoma, respectively. The presence of active infection is a contraindication to living donation. Fully treated syphilis, tuberculosis, and latent cytomegalovirus (CMV) do not preclude donation.

Potential kidney donors should be screened for both personal and family history of cancer. They should undergo standard age-appropriate screening tests as recommended by the American Cancer Society and equivalent international organizations. Certain types of cancer have characteristics that would exclude any person with a prior history from donation. These cancers include those that are considered incurable, known to

have a lengthy disease-free interval before possible recurrence, or reported to have the potential for increased virulence in the immunocompromised patient. A history of melanoma, renal cell carcinoma or urologic malignancy, choriocarcinoma, hematologic malignancies, gastric cancer, lung cancer, breast cancer, Kaposi sarcoma, or monoclonal gammopathy precludes living donation. The effects of prior treatment of the malignancy on the prospective donor's renal reserve as well as potential nephrotoxicity from future treatment in case of recurrence are additional concerns. Donation may be acceptable if the specific cancer (e.g., in situ squamous cell skin cancer or cervical carcinoma) is deemed cured and the potential for transmission is excluded. Oncology consultation is advisable.

MEDICAL CLEARANCE FOR SURGERY

Certain characteristics and medical problems in prospective donors potentially increase the risks for postoperative complications and preclude donation. In general, underlying problems such as coronary artery disease (even if corrected), cerebrovascular disease, and significant chronic pulmonary disease increase the risk for having perioperative morbidity and contraindicate donation. Potential donors with multiple risk factors for coronary artery disease warrant noninvasive screening. Suggested cardiovascular testing of potential living donors is outlined in Table 6.7.

Potential donors who smoke should be instructed to stop for at least 4 weeks before the surgical procedure to decrease pulmonary complications and strongly urged to quit permanently to decrease future health risks. Some transplantation centers will not accept a potential donor who continues to smoke. Pulmonary function testing for prospective donors is not routinely indicated unless the history or physical examination is suggestive of lung disease.

Coagulation Disorders

A history of hypercoagulability significantly increases the risk for perioperative thrombotic complications and may contraindicate donation. Persons with a family history of thrombotic disease or personal history of one episode of venous thrombosis or recurrent miscarriage should be screened for the presence of risk factors that would increase the risk for future events. Common factors to be considered include abnormal activated protein C resistance ratio associated with factor V Leiden mutation; lupus anticoagulant or anti-cardiolipin antibody; or prothrombin gene mutation (FII-20210). However, a person heterozygous for factor V Leiden mutation without previous thrombotic disease is not necessarily excluded from donation because the risk for complication is low. Individuals who have had a first confirmed episode of DVT and who are heterozygous or homozygous for the Leiden factor V mutation demonstrate, respectively, a 7-fold and an 80-fold increase in the

relative risk for DVT. Appropriate perioperative prophylaxis to prevent thrombotic

complications, as well as discussion of the significance of this abnormality, is advised. Disorders requiring chronic anticoagulation contraindicate donation.

TABLE 6.7 Suggested Cardiovascular Evaluation of a Potential Living Donor

Exclusion Criteria as Donor

- Diabetes mellitus
- Untreated and/or symptomatic coronary artery disease
- Dilated cardiomyopathy
- Compensated or decompensated heart failure
- Untreated and/or clinically significant arrhythmias
- Untreated and/or symptomatic clinically significant valvular heart diseases

Indication for Cardiac Structural Evaluation with Two-Dimensional Echocardiogram

- Abnormal cardiac murmurs
- History of syncope, dizziness, palpitations, or short of breath
- Indications for Holter monitoring

  — History of arrhythmias or possible arrhythmias

  — History of syncope, dizziness, or palpitations

Indications for Cardiac Stress Testing*

- Older age (>45 years in men or >55 years in women). May vary, depending on:
  - Donor's routine activity level
  - History of smoking
  - Family history of premature coronary artery disease

  History of dyslipidemia (should be included in risk factor

- assessment; dyslipidemia alone is not an indication for cardiac stress testing)*

- History of hypertension

- Abnormal electrocardiogram (left ventricular hypertrophy, left bundle branch block, ST-T abnormalities)

* One or more of the indications listed or at the clinician's discretion.

LONG-TERM POSTNEPHRECTOMY ISSUES

Renal Function

Within days to weeks after uninephrectomy, hyperfiltration in the remaining kidney increases the GFR to about 75% to 80% of predonation value. The amount of compensation is dictated by age-related renal reserve. Follow-up studies among donors up to 35 years after nephrectomy attest to the long-term safety of the procedure. Decline in renal function parallels that of age-related declines in healthy individuals with two kidneys. Urine albumin excretion, attributable to single nephron hyperfiltration from reduced renal mass, may be elevated but is usually low grade and not associated with a higher risk for renal dysfunction. A systematic review, meta-analysis, and meta-regression study conducted by the Donor Nephrectomy Outcomes Research (DONOR) Network (see Garg and colleagues in “Selected Readings”) revealed that 7 years after donation, the average GFR was 86 mL per minute, and the average urine protein

was about 150 mg/per day. Studies comparing donors to controls reveal that urinary protein excretion is higher in donors compared with controls a decade after donation and becomes more pronounced with time. Nonetheless, the increase in protein excretion is not clinically significant in most patients. An initial decline in GFR was not accompanied by accelerated loss over a subsequent 15 years of follow-up.

Long-Term Risk for Chronic Kidney Disease and End-Stage

Renal Disease The

risk for future development of chronic kidney disease and subsequent progression to ESRD in the remaining single kidney has always been a major concern for prospective donors and their advocates. At long-term follow-up, unilateral nephrectomy reduces renal function by about 20%. Similar to the nondonating population, an additional 5 mL per minute loss in GFR per decade occurred after donating. Data on the effects of nephrectomy on the progression and complications of ESRD are lacking. Several large follow-up studies report an incidence of ESRD in the donor population, which is essentially the same as in matched cohorts of the general population. The United Network for Organ Sharing (UNOS) database has recorded since 1987 an incidence of about 0.04% of living kidney donors who have been listed for a kidney transplantation (similar to the 0.03% incidence in the general U.S. population). In a follow-up study of 3698 donors who donated between 1963 and 2007, ESRD developed in 11 donors, a rate of 180 cases per 1 million persons per year, compared with a rate of 268 per 1 million persons per year in the general population (see Ibrahim et al in "Selected Readings"). Most donors who have become recipients have been related donors, suggesting that there may have been unrecognized familial renal disease or risk factors. Young African American donors may also be at increased risk.

Hypertension

The incidence of hypertension requiring treatment increases with time following kidney donation, but most studies suggest a similar frequency compared with an age-matched population. A meta-analysis of more than 5000 living kidney donors with an average follow-up of 7 years revealed that the donors may experience a 5-mm Hg increase in blood pressure (over that anticipated with normal aging) within 5 to 10 years after donation; this finding is clinically insignificant in most patients. Nonetheless, whether an increase in blood pressure from kidney donation increases cardiovascular disease risk remains to be defined.

Long-Term Mortality

Living kidney donation appears to have no apparent adverse effect on survival at long-term follow-up, although it should be understood that the data supporting this conclusion are, by necessity, based on the demographics of the donor population more than 20 to 30 years ago, an era when the criteria by which donors were accepted for donation may have been more stringent than is currently practiced at some centers. Indeed, the donor profile has changed over time and may now include donors with isolated medical abnormalities (IMAs) such as borderline or mild hypertension, obesity, dyslipidemia, or metabolic syndrome. With the expansion of living donor criteria, it is of great importance for the evaluating physician to minimize or modify the donor's current health risks, educate the donors of their potential increased risks, and emphasize to the donors the importance of maintaining a healthy lifestyle and regular

medical follow-up following donation.

PREGNANCY

Women of childbearing age should be told that there is no evidence that unilateral donor nephrectomy has a deleterious effect on fertility, prenatal course, or outcome of future pregnancies. It is advisable to delay pregnancy for at least 6 months to allow for maximal compensatory hypertrophy of the single kidney and prudent to obtain early prenatal care with screening for hypertension, urinary abnormalities, and renal function. There is no evidence to support an increased risk for renal-related complications as a consequence of obstruction from a gravid uterus. Therefore, the desire for future pregnancy does not need to dictate the selection of which kidney to use for donation.

EMPLOYMENT AND INSURANCE

Most donors can return to their prior employment without limitation. In the United States, the federal government and many private employers provide employees with up to 30 paid working days after organ donation. Donors engaged in heavy physical labor may have some difficulty after open nephrectomy; this possibility should be discussed before the procedure. In general, kidney donors do not have insurability issues in terms of higher rates or an inability to obtain insurance. Any problems encountered are most likely attributable to the insurance company's incomplete knowledge regarding donor outcome and should prompt contact and education by the transplantation program. Most branches of the military will allow a person on active duty to donate a kidney and remain in the service, but it may affect the future ability to participate in all aspects of the military. A recent history of donation may preclude military recruitment. Future career plans should be discussed with prospective donors.

LONG-TERM MEDICAL CARE

Recommendations for future medical care and risk modification for a kidney donor are not much different than those for the general population. Routine checkups, cancer screening appropriate for age, regular aerobic exercise, weight reduction, tobacco avoidance, and excessive alcohol abstinence should be emphasized. Kidney donors with established medical issues before donation, such as mild hypertension, history of nephrolithiasis, or obesity, should have more frequent follow-up, and it could be argued that they should not be donors if they do not have access to such follow-up. Donors should be discouraged from using high-protein diets for weight loss or protein supplements for body building because they may contribute to hyperfiltration injury. They should be advised to avoid long-term regular use of nonsteroidal anti-inflammatory drugs or acetaminophen, because of their association with renal insufficiency.

PART II. SURGICAL ISSUES IN LIVING KIDNEY DONATION

In addition to the medical and psychosocial evaluation of the prospective donor detailed in Part I, the evaluation of the prospective donor by the donor surgical team is an intrinsic component of the kidney donor evaluation process. Generally, the surgical consultation represents the final medical visit for the donor candidate after the preliminary evaluation has been completed. It allows for appropriate patient selection, choice of the kidney for donation, and selection of the surgical technique to be employed and it ensures that the patient is fully informed of the risks of kidney donor surgery. The relative advantages and disadvantages of open and laparoscopic nephrectomy are summarized in Table 6.8.

TABLE 6.8 Relative Advantages and Disadvantages of Open Versus Laparoscopic Living Donor Nephrectomy

	Open	Laparoscopic
Safety record	Established international long-term record	Safety comparable to open nephrectomy with increasing surgical expertise; reoperation with or without conversion rates depends on surgeon expertise
Surgical complications	Retroperitoneal approach minimizes potential abdominal complications	Pneumoperitoneum may compromise blood flow
		Disadvantages: tendency to have shorter renal vessels and multiple

		arteries Advantages: magnified view of renal vessels
Scar formation	Long surgical scar with the potential for hernia and abdominal wall asymmetry	Minimal surgical scar: better cosmetic appearance
Operative time	2-3 hours	3-4 hours (increased warm ischemia time)
Postoperative pain	Occasionally persistent	Less postoperative pain (less analgesics required)
Hospital stay	4-5 days	1-2 days
Return to work	6-8 weeks	3-4 weeks
Recipient outcomes: graft function, rejection rate, urologic complications, patient and graft	Comparable	Comparable

survival		

Data based on a systematic review of 69 studies through PubMed searches (readers are referred to Shokeir in “Selected Readings”).

HISTORY AND PHYSICAL EXAMINATION

The surgical evaluation provides an additional opportunity to identify issues that have not been revealed during prior visits as well as to focus on the details specific to donor surgery. The recipient's identity, the recipient's relationship to the donor, and the cause of the recipient's renal failure are reviewed. It is not uncommon for new issues to be raised at this visit, or for the social situation of the donor to have changed in a way that may affect the donor's candidacy or willingness to be a donor. Particular attention is focused on whether the patient has any urologic history, including as gross hematuria, nephrolithiasis, pyelonephritis, renal cysts, or renal tumors.

The physical examination includes measurement of vital signs and allows for confirmatory measurements of height and weight for the computation of the patient's BMI. Particular attention is paid to the abdominal examination to evaluate the patient's body habitus and to document any prior surgical scars relevant to the surgical approach. This simple evaluation is essential to identify patients appropriate for minimally invasive donor surgery.

Review of Imaging

Donor imaging is also discussed in Chapter 13. CT-based imaging is routinely used to evaluate a potential donor's renal anatomy. The 64-slice multidetector (64-MDCT) urogram and angiogram phases generate high-quality images that allow for identification of intra-abdominal findings that may preclude donation; prompt further investigation; assess renal size; assess parenchymal and collecting system anatomy; and define the vascular anatomy of the renal units. These images can be obtained using a less invasive approach than traditional arteriography and intravenous urography.

Renal Nonvascular Anatomy and Abdominal Abnormalities

Incidental intra-abdominal pathology is often discovered at the time of the MDCT imaging. Adrenal nodules are detected in a small portion of patients and present a clinical challenge. If the adrenal lesions meets CT criteria for benign adenoma and a functional metabolic workup is negative, proceeding with donation is reasonable.

Multiple phase MDCT images demonstrate the size of each kidney and the amount of

renal parenchyma. Rapid symmetrical uptake of intravenous contrast, combined with prompt excretion and drainage, documents the relative renal function and can obviate the need for routine renal scans. Donors found to have disparities in renal size, contrast uptake or excretion, or renal scars may be further studied with a MAG3 renal scan to ensure adequate renal function (see Chapter 13). The affected kidney is then chosen to ensure the donor is left with the highest functioning renal unit. Delayed urogram phases also document the anatomy of the collecting system of each kidney and ureter. The identification of a calyceal diverticulum, asymptomatic hydronephrosis with ureteropelvic junction obstruction, or complete and partial ureteral duplication may alter the surgical approach.

About 30% of kidneys evaluated using MDCT technology have incidental renal pathology such as low-density lesions, renal cysts, and calyceal calcifications. This information does not necessarily preclude donation. In a series of more than 850 laparoscopic and open donor nephrectomies from 2000 to 2007, about 20% of patients were found to have incidental renal findings such as low-density lesions considered “too small to characterize” on preoperative evaluation. Large or complex renal cysts require attention and may necessitate removal of the affected kidney.

Calyceal calcifications are frequently identified with high-resolution CT-based imaging. Patients with a history of nephrolithiasis and those found to have bilateral, multiple unilateral, or large renal stones are not considered candidates for donor nephrectomy. Donor candidates found to have a single small asymptomatic calcification, particularly older donor candidates, undergo a thorough metabolic workup as detailed in Part I. If no abnormalities are detected, it is reasonable to proceed with donation, removing the affected kidney.

CT-based imaging can also supplement the patient selection process by elucidating the amount of perirenal fat and whether the kidney “rests” on the psoas muscle. This information can be used to select higher BMI donors that will still be amenable to a laparoscopic approach. This becomes particularly important in patients with complex vascular anatomy because the amount of perirenal fat can indicate significantly more and challenging dissection within the hilum. Figure 6.2 illustrates three patients with BMI values of 33 but varying amounts of perirenal fat.

FIGURE 6.2 Three patients with a calculated body mass index of 33 and varying amounts of perirenal fat.

Renal Vascular Anatomy

Vascular anatomy has become increasingly relevant to the surgical evaluation with the increasing adoption of laparoscopic approaches to kidney donor surgery, and 64-MDCT has demonstrated impressive sensitivity to identify small vascular structures. The increased resolution of 64-MDCT, along with three-dimensional reconstructions, will likely increase the operative safety as well identify small capsular and polar arteries such that attempts can be made to preserve these structures if indicated (Fig. 6.3). This imaging information can then be used to determine the appropriate kidney for donation. The left kidney is the preferred organ because of the longer length of the renal vein. It is routine to select the left kidney when one or two left renal arteries are identified. A right nephrectomy may be preferred when the left kidney is found to have more than two arteries. Arterial anatomy that is more complex is reviewed on an individual basis. Venous anatomy rarely precludes left-sided laparoscopic donor nephrectomy.

Risks of Surgery

Perhaps the most important aspect of the surgical visit for potential donors is a thorough review of the risks, benefits, and alternatives to kidney donation. It is critical for the patient to be fully informed of the risks of undergoing surgery and to have realistic expectations of the hospital and postoperative course. Occasionally, potential donors who have completed their medical and psychosocial evaluation will express reservations when the details of donor surgery are discussed. If necessary, a medical "alibi" can be provided to ensure that the potential donor does not feel undue pressure to proceed with the process that may have taken some time to complete and may be close to fruition.

When reviewing the risk for surgery, the risks common to the general anesthesia, including heart attack, stroke, blood clot, and pulmonary embolus, are discussed. The risk for death in healthy kidney donors is extremely low (estimated at 3 to 4 cases per 10,000 nephrectomies) but cannot be ignored. There may be bleeding, need for blood transfusion, wound infection, and postoperative pain. There is also a risk for injuring organs adjacent to the operative field. Specific to right donor nephrectomy, these structures include the liver, duodenum, colon, diaphragm, and pancreas. For a left-sided procedure, the structures at risk include the colon, small intestine, pancreas, spleen, and diaphragm. These injuries may require repair if identified at the time of surgery or

---

may necessitate reoperation if identified after surgery. Cases of chylous ascites, intra-abdominal adhesions, and internal hernia formation have been reported. Minor risks include the development of wound infections, subcutaneous hematoma formation, and traumatic neuropathy, from either the incision or operative positioning. Risks particular to laparoscopic approaches include increased operative time and the

occasional need to convert to an open procedure typically because of excessive bleeding.

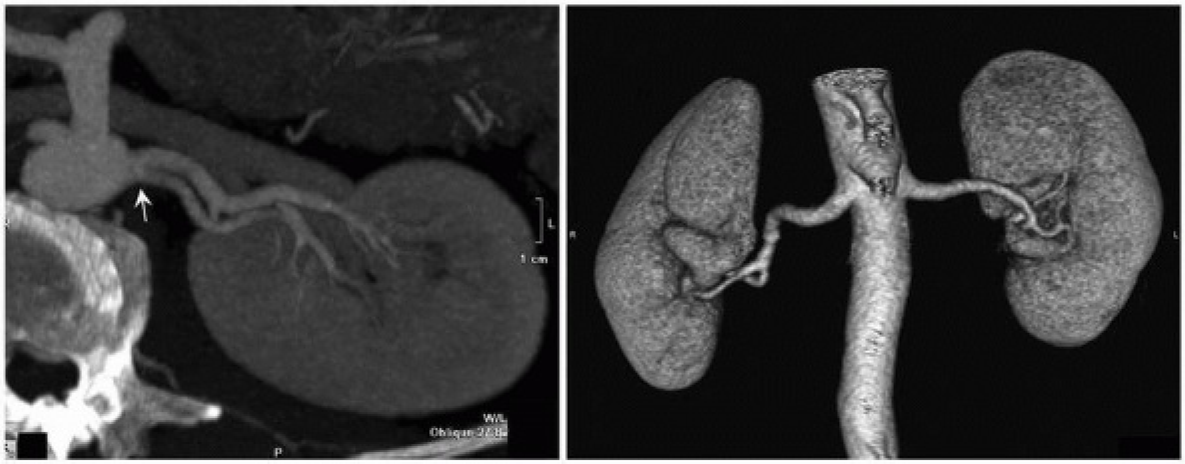


FIGURE 6.3 Example images from multidetector computed tomography illustrating an early bifurcation of a renal artery (*arrow*) and an example of three-dimensional renal reconstruction.

SURGICAL TECHNIQUES FOR LIVING DONOR NEPHRECTOMY

The introduction of laparoscopic living kidney donation has been a major advance in organ donation. First introduced with some trepidation in select centers in the mid-1990s, these procedures are now the preferred surgical approach in most large transplantation programs in the United States. Programs that offer the procedure have higher rates of living kidney donation. The major benefits of laparoscopic techniques include significant reduction in surgical pain, postoperative convalescence, and recovery time. As a result, laparoscopic donor nephrectomy has been responsible for expanding the pool of living donors and may account for the increased popularity and frequency of living donation. Long-term renal function is not different between open nephrectomy and laparoscopic nephrectomy. About 75% of living donor transplant nephrectomies performed in the United States employ laparoscopic techniques. Laparoscopic donation is much less commonly applied in Europe, but its popularity is steadily increasing.

Laparoscopic Nephrectomy—Surgical Technique

Laparoscopic techniques require specially trained surgical staff. For laparoscopic donor nephrectomy, the donor is placed in the flank position, and a pneumoperitoneum is established with a Veress needle. A 5-mm visual trocar is placed 3 fingerbreadths below the xiphoid at the lateral border of the rectus muscle under direct vision. A 5-mm laparoscope is then inserted. Under direct vision, two additional 5-mm trocars are

inserted along the lateral border of the rectus muscle, and a fourth 5-mm trocar is placed laterally at the level of the tip of the 12th rib. The surgery then proceeds as outlined next.

First, the white line of Toldt is incised down to the level of the iliac vessels in order to reflect the colon medially. The posterior peritoneum is then incised toward the crus of the diaphragm, mobilizing the spleen (for left-sided nephrectomy) or the liver (for right-sided nephrectomy) from the upper pole of the kidney. Lateral retraction is then provided through the lateral trocar in order to displace the adrenal gland medially and complete the dissection of the upper pole of the kidney. The renal hilum and gonadal vein are then identified. The gonadal vein is then dissected, clipped, and transected, a practice that does not increase the incidence of ureteral strictures in recipients. A plane lateral to the gonadal vein is then created, freeing the ureter down to the level of the iliac vessels. The renal hilum is elevated, and the renal artery and vein are carefully identified and circumferentially isolated. The remaining posterior and lateral attachments are then divided. Intraoperative mannitol is administered in two 15g doses, with the first dose given at the start of surgery and the second dose delivered about 15 minutes before the ligation of the renal hilum. A horizontal midline incision, just large enough to accommodate the kidney, is made at the pubic hair line for an improved postoperative cosmetic result. The fascia is then incised vertically, and the midline is identified. A 15-mm trocar is placed through the superior portion of this incision to accommodate a vascular stapling device. The renal arteries, veins, and ureter are then divided with a vascular stapler, and the kidney is placed in an entrapment sack. Heparin dosing, with protamine reversal, is used in some programs but may be unnecessary.

The two bellies of the rectus muscle are spread to allow for removal of the kidney and sack. After removal, the kidney is then placed in frozen saline slush, and the vascular staples are excised. The renal arteries are flushed with cold heparinized lactated Ringer solution.

The hand-assisted laparoscopic technique employs a relatively small abdominal incision to allow the introduction of the surgeon's hand to supplement the laparoscopic procedure and permit rapid, atraumatic removal of the kidney. Laparoscopic techniques can be rapidly converted to open nephrectomy in the event of uncontrolled bleeding or unforeseen anatomic abnormalities.

Open Nephrectomy

The traditional method for removing a kidney from a living donor has been an open surgical technique, using a modified flank incision. In select cases in which the donor has issues precluding laparoscopic access (e.g., significant prior abdominal surgery), or in some cases of complex vascular anatomy, an open surgical approach is preferred. Some centers advocate the use of open donor surgery for pediatric recipients, although

the age of the recipient is not universally considered an indication for open renal procurement. Most donor surgeons use an extrapleural and extraperitoneal approach, just above or below the 12th rib. The kidney must be carefully dissected to preserve all renal arteries, renal veins, and the periureteral blood supply. Excessive traction on the renal artery is avoided to prevent vasospasm. After the renal vessels are securely ligated and divided, the kidney is removed and placed in a basin of frozen saline slush to decrease renal metabolism. The renal arteries are cannulated and flushed with heparinized solution as with laparoscopic donor nephrectomy.

Postoperative Management

In the operating room, donor nephrectomy patients may be given their first dose of ketorolac for effective pain control. Ketorolac is administered in 30mg dosing every 6 hours for up to 48 hours. Its routine use decreases morbidity following donor nephrectomy without compromising renal function. For laparoscopic cases, the oral gastric tube is removed before extubation. The patient is transferred to the recovery room with a urethral catheter to gravity drainage. An aggressive bowel preparation is routinely employed before surgery. This allows the patient to be started on sips of clear liquids on the evening of the day of surgery. The diet is advanced to a full liquid diet on the morning of postoperative day 1, and to a regular diet thereafter as tolerated. Early ambulation is encouraged, as is aggressive pulmonary toilet. The combination of early mobilization and ketorolac-based analgesia during the first 48 hours facilitates early return of bowel function and shorter hospital stays. The average hospital stay after laparoscopic donor nephrectomy is 11/2 days. Most donors can return to all but the most strenuous exercise or work by 3 to 4 weeks. Laparoscopic procedures are associated with a faster recovery, less postoperative pain, and a full recovery in about 3 to 4 weeks. Complete recovery for open donor nephrectomy takes 6 to 8 weeks, although some donors complain of incisional pain for 2 to 3 months.

PART III. INNOVATIVE AND CONTROVERSIAL ASPECTS OF LIVING KIDNEY DONATION

ISOLATED MEDICAL ABNORMALITIES AND RISK ASSESSMENT

Donors have typically been accepted or rejected based on the evaluating physician's perception of safety for the donors. The most common reasons for declining an otherwise acceptable donor are mild hypertension and asymptomatic urinary abnormalities, because of the fear of increased risks for the development

---

of ESRD. Indeed, no person can, or should, be told that the risk is nil. All risks are relative, and the risk for developing chronic renal failure in the face of mild hypertension or isolated microscopic hematuria appears to be low, with a reported incidence between 1 of 100 and 1 of 10,000 donations—an incidence that is considerably

lower than for the general population. It has been suggested that rather than declining such borderline patients from the outset, an attempt should be made, based on available data on the demographics of renal disease, to give the potential donor an estimate of his or her risk and to permit the donor, within reasonable limits and after careful education, to decide on an acceptable degree of risk. Risk assessment is not absolute, however, and should be age adjusted: the finding of mild hypertension or a kidney stone in a 20-year-old will clearly be of much greater concern than similar findings in a 60-year-old. Young donors with isolated medical abnormalities are generally excluded from donation.

BIOLOGICALLY UNRELATED DONORS

The number of living unrelated donor transplantations performed in the United States is steadily increasing and as of January 2009 constituted close to 40% of the living donors in the United States, a number about twice that of the previous decade. Most of these donors are "emotionally related" and have an apparent or easily documented close and long-standing relationship with the recipient (spouse, significant other, close friend, adopted sibling). During the past decade, an increasing number of prospective donors with a much more casual relationship with the recipient (e.g., coworkers, acquaintances, members of faith community) or with little or no relationship to the recipient (e.g., solicited through the Internet, media appeals, paired exchange) are being performed in the United States, and about half of unrelated donors fall into this category, a fourfold increase over the previous decade.

Nondirected Donors

The biologically unrelated donors referred to above all donate to a specific individual who is known to them. A nondirected donor is one who comes forward to donate a kidney to someone unknown to them. The term *altruistic donor* (or *Good Samaritan donor)* is often used to describe these donors, but altruism is not a measurable factor and may certainly be present in all donors to a varying degree. Generally, the recipient of a kidney from a nondirected donor is a patient on the deceased donor waiting list with a compatible blood type, the most waiting time, and negative crossmatching (see Chapter 4). Nondirected donors may also play a critical role in living donor exchange programs (see Living Donor Exchange). The nondirected donors do not know or select, and may never meet, the recipient and therefore may not observe or enjoy the recipient's gain of health following the kidney transplantation. The motives of altruistic donors are sometimes looked on with skepticism or suspicion. Public surveys in the United States report that up to 50% of the adult population would be willing, in principle, to anonymously donate a kidney to a stranger.

The evaluation of nondirected donors and of all donors whose relationship with the recipient is a tenuous one must emphasize a careful psychosocial examination to fully explore the motivation for donation and identify unrealistic expectations,

misperceptions, and covert depression. Guidelines for the triage and evaluation of nondirected donors have been developed (see Chapter 17, Table 17.1 and Adams and coworkers in “Selected Readings”). Less than 10% of persons who contact transplantation programs with a view to donating in a non-directed fashion actually become donors. Nonetheless, nondirected donors represented about 1.5% of all living donors in the United States as of January 2009.

HLA-SENSITIZED AND ABO-INCOMPATIBLE DONOR AND RECIPIENT

During the past decade, several innovative protocols have been adopted to overcome transplantation across a positive crossmatch or ABO blood group barrier (see Chapter 3). Protein A immunoadsorption, high-dose intravenous immune globulin (IVIG), low-dose IVIG in combination with plasmapheresis, rituximab, and splenectomy, used alone or in combination, can abrogate a positive crossmatch and enhance the chance of a highly sensitized patient to receive a crossmatch-negative organ. Similar strategies can be used for ABO-incompatible donors and are particularly effective when the titer of blood group antigens is low (see Chapter 7, Fig. 7.2)

LIVING DONOR EXCHANGE

Paired Living Donor Exchange

A simple paired donor exchange has been proposed as a solution for donor-recipient pairs with ABO incompatibility. In this scheme, two or three incompatible donor-recipient pairs are matched to other pairs with a complementary incompatibilities (e.g., blood group A to B couple exchanges with blood group B to A couple; Fig. 6.4).

Living and Deceased Donor List Exchange

The UNOS allocation algorithm for deceased donor kidneys (see Chapter 4) permits a variance whereby an incompatible living donor may donate a kidney to the next compatible, third-party recipient who is at the top of the deceased donor waiting list. In turn, the initially intended, but incompatible, recipient is given priority on the deceased donor waiting list, thereby reducing the anticipated waiting time for a deceased donor organ. Although these innovative solutions provide potential options for motivated but incompatible donors, the practical difficulties with these options mandate that whenever possible, a compatible donor be found. Type O donors are less likely to participate in paired kidney donation because they are able to donate to recipients of any blood type. Hence, deceased donor kidneys of the O blood type become the main source for the exchange recipient. Typically, this exchange involves a

blood type A donor and a type O recipient. The type A donor gives his or her kidney to the type A recipient who is at the top of the deceased donor waiting list. In turn, the living donor's intended type O recipient is given priority on the deceased donor waiting list. Although such a “living and deceased donor exchange” program has met its utilitarian goal—namely, allowing more recipients to undergo successful transplantation by expanding the pool of compatible live donors—it has been criticized on ethical grounds because it creates a disadvantage for the type O list candidates who are waiting for a type O deceased donor kidney. In practice, candidates who were bypassed on the day the allocation priority was granted to the exchange recipient had only to wait several weeks to months longer than they would have without the exchange process.

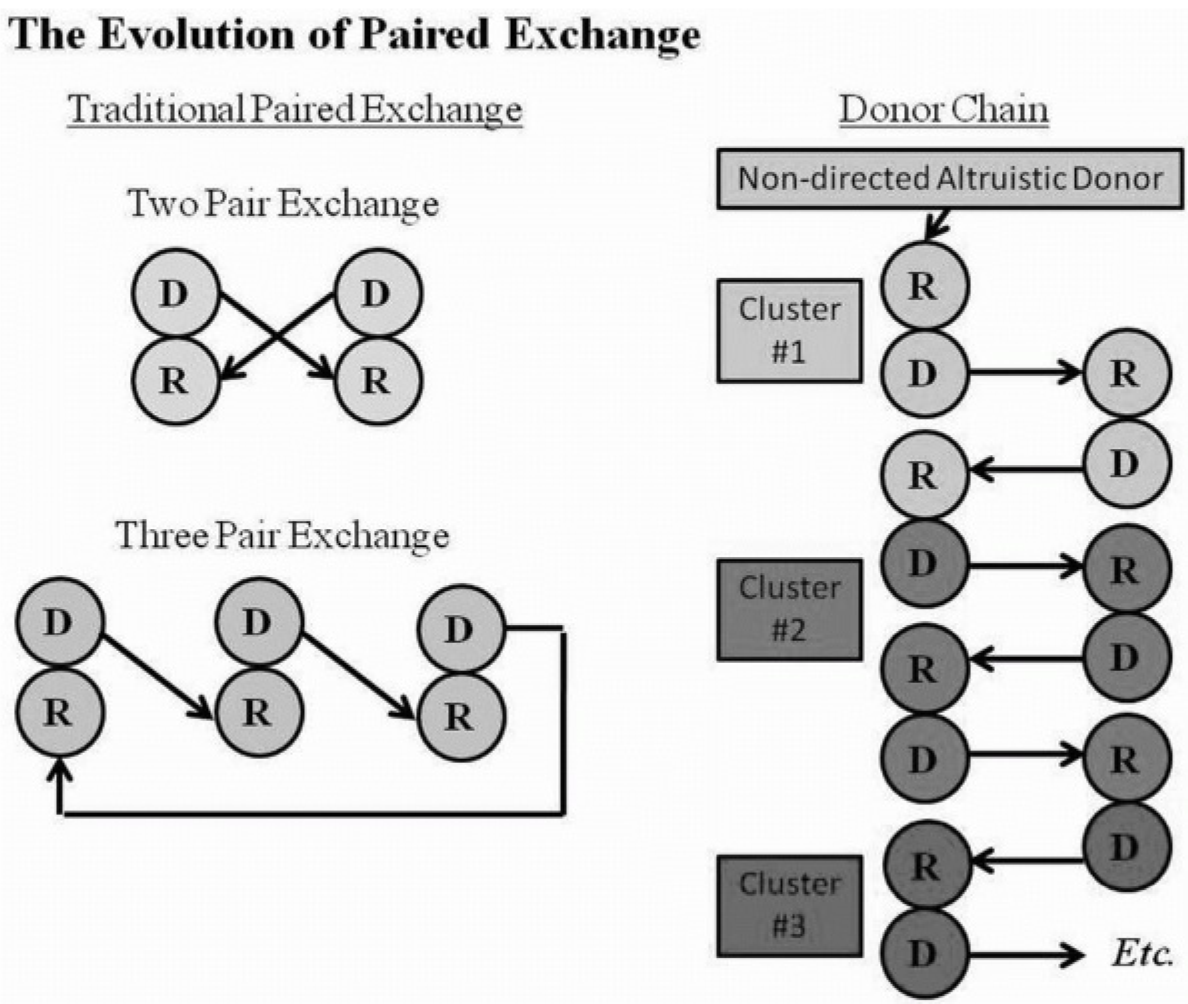


FIGURE 6.4 The evolution of paired exchange. (Courtesy of Garet Hill of the National Kidney Registry.)

Domino-Paired Kidney Donation

To achieve the optimal benefit from nondirected donors, a strategy has been developed whereby the donated kidney is matched to a recipient who has an intended, but

incompatible, living donor. In turn, the recipient's incompatible living donor donates his or her kidney to the next compatible patient on the deceased donor waiting list, generating a domino effect. Nondirected donors can donate to a recipient with an incompatible donor and hence generate “clusters” or “chains” of living donor transplants with “bridge” donors perpetuating the chain (Fig. 6.4).

Local and regional living donors exchange programs have been developed, and some countries have developed national sharing programs. These programs use sophisticated computer algorithms to generate the best matches and even permit highly sensitized patients to be matched. A national exchange program is being developed in the United States under the auspices of UNOS. One of the “taboos” that has been broken in these programs is the “shipping” of living donor kidneys from one center to another, in a manner similar to the transportation of deceased donor kidneys. The short cold-ischemia times that such shipping entails does not appear to have an unfavorable effect on outcome.

PAID DONATION

In the United States, the sales of human organs involving either direct monetary exchange or exchange of donor organ for valuable property violates the National Organ Transplant Act of 1984. Similar legislation is in place internationally, and major professional transplantation organizations prohibit such payment. Reimbursement for expenses related to the donation process such as for traveling and lodging is not prohibited, although a formal mechanism to make such reimbursements is not available in the United States, a factor that could act as a disincentive to donation for some potential donors. Iran is currently the only country in which paid donation is officially sanctioned, almost all the donors are poor and uneducated and follow-up studies have shown that their lives are not improved.

Despite the legal constraints on organ sales, commerce in kidney transplantation is a common phenomenon in many parts of the world and, in some cases, has been linked to criminal activity. The donors are typically poor or

---

under great financial stress, the recipients are often wealthy or come from other wealthier countries, and “middlemen” or “brokers” are often involved.

Arguments against paid donation express concern for the exploitation of the poor, commodification of the human body, and the documented negative impact on both living and deceased donation. Arguments made for allowing paid donation claim that the money paid to poor donors would have a significant positive impact on their quality of life, that paid donors are entitled to use their bodies as they see fit, that the risks of the procedure are small, and that there is no other way to address the organ donor shortage. Available data on the outcome of organ vending for the donors indicates that most of them have a poor psychosocial outcome. Recipients of vended organs are subject to an increased risk for complication, particularly infection, likely as a result of

a breakdown of trust and honesty that is a byproduct of the commercialization of organ donation. Evidence from several countries has shown that commercialization of organ donation comes at the expense of programs for related and unpaid living unrelated donation.

An important distinction between “travel for transplantation” and “transplant tourism” is made in the Declaration of Istanbul (see Appendix). Physicians should discourage patients from engaging in transplant tourism and should inform them of its legal, ethical, and medical consequences. When faced with a patient who has returned to his or her country of origin after a paid donation, optimal care should be provided in a professional and nonjudgmental manner.

LIVING DONOR REGISTRY

Long-term follow-up of transplant recipients is one of the responsibilities of transplantation programs. In the United States, follow-up data are submitted to UNOS and are available for scientific analysis and to the general public. Until recently, no such follow-up has been mandated for living donors. Concerns about the adequacy of safety data on living donation have been raised, and it has been suggested that complications following live donor nephrectomy are underreported and underestimated.

Reports of morbid experiences in live organ donors have generated a consensus that formal follow-up of living donors should be instigated. Such follow-up might permit more substantive answers to questions about the safety of donor evaluation and acceptable practices. Since June 2006, in the United States, compliance with standards for transplantation programs to perform living donor kidney transplantation has been under the authority UNOS. A requirement to report all living donor deaths and significant medical events has been implemented. The development of a national living donor registry is being considered. A registry would be a valuable source of information, but it is unlikely that it would significantly change our current understanding of the risks and benefits that are intrinsic in the living donor kidney process.

THE DOCTOR-PATIENT RELATIONSHIP IN LIVING KIDNEY DONATION

It is fitting to end this chapter by quoting a statement that cannot be overemphasized.

> “At all stages of the evaluation and transplant process, the donor is as legitimately considered to be a patient as the transplant recipient….”
>
> Dew MA, Jacobs CL, Jowsy SG, et al. Guidelines for the psychosocial evaluation of living unrelated kidney donors in the

United States. Am J Transplant 2007;7:1047-1054.

The donor is entitled to the same degree of advocacy and mutual trust as is the recipient. A successful outcome to a living donor transplant requires a good outcome for both the donor and the recipient, with outcome being assessed in its broadest sense, medically and psychosocially, short-term and long-term.

Selected Readings

Adams P, Cohen DJ, Danovitch GM, et al. The nondirected live-kidney donor: ethical considerations and practice guidelines: a national conference report. Transplantation 2002;74:582-587.

Boudville N, Prasad GVR, Knoll G, et al. Meta-analysis: risk of hypertension in living donors. Ann Intern Med 2006;145:185-196.

Breda A, Bui M, Liao P, Schulam P. Association of bowel rest and ketorolac analgesia with short hospital stay after laparoscopic donor nephrectomy. Urology 2007;69:828-831.

Breda A, Veale J, Liao J, Schulam P. Complications of laparoscopic living donor nephrectomy and their management: the UCLA experience. Urology 2007;69:49-52.

Danovitch GM. The doctor-patient relationship in living donor kidney transplantation. Curr Opin Nephrol Hypertens 2007;16:503-505.

Davis C. Evaluation of the living kidney donor: current Perspectives. Am J Kidney Dis 2004;43:508-530.

Davis C, Delmonico FL. Living-donor kidney transplantation: a review of the current practices for the live donor. J Am Soc Nephrol 2005;16:2098-2110.

Delmonico F, Council of the Transplantation Society. A report of the Amsterdam Forum on the Care of the Live Kidney Donor: data and medical guidelines. Transplantation 2005;79:S53-S56.

Delmonico FL, Dew MA. Living donor kidney transplantation in a global environment. Kidney Int 2007;71:608-614.

Dew MA, Jacobs CL, Jowsy SG, et al. Guidelines for the psychosocial evaluation of living unrelated kidney donors in the United States. Am J Transplant 2007;7:1047-1054.

Fehrman-Ekholm I, Norden G, Lennerling A, et al. Incidence of end-stage renal disease among live kidney donors. Transplantation 2006;82:1646-1648.

Garg AX, Muirhead N, Knoll G, et al. Proteinuria and reduced kidney function in living kidney donors: a systematic review, meta-analysis, and meta-regression. Kidney Int 2006;70:1801-1810.

Garg AX, Prasad G, Thiessen-Philbrook H, et al. Cardiovascular disease and hypertension risk in living kidney donors: an analysis of health administrative data in Ontario, Canada. Transplantation 2008;86:399-406.

Gore J, Danovitch G, Litwin M, Pham T, et al. Disparities in the utilization of live donor renal transplantation. Am J Transplant 2009;9:1124-1129.

Ibrahim H, Foley R, Tan L, et al. Long-term consequences of kidney donation. N Engl J Med 2009;360:459-469.

Kok NF, Weimar W, Alwayn IP, et al. The current practice of live donor nephrectomy in Europe. Transplantation 2006;82:892-897.

Lam J, Breda A, Schulam P. Is laparoscopic donor nephrectomy the new standard? Nat Clin Pract Urol 2007;4:186-187.

Montgomery R, Katznelson S, Bry W, et al. Successful three-way kidney paired donation with cross-country live donor allograft transport. Am J Transplant 2008;10:2163-2168.

Ommen ES, Winston JA, Murphy B. Medical risks in living kidney donors: absence of proofs is not proof of absence. Clin J Am Soc Nephrol 2006;1:885-895.

Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 2009;20:205-212.

Pham PC, Wilkinson AH, Pham PT. Core curriculum in nephrology: Evaluation of the potential living kidney donor. Am J Kidney Dis 2007;50:1043-1051.

Raman S, Pojchamarnwiputh S, Muangsomboon K, et al. Utility of 16-MDCT angiography for comprehensive preoperative vascular evaluation of laparoscopic renal donors. J Roentgenol 2006;186;1630-1634.

Raman S, Pojchamarnwiputh S, Muangsomboon K, et al. Surgically relevant normal and variant renal parenchymal and vascular anatomy in preoperative 16-MDCT evaluation of potential laparoscopic renal donors. AJR Am J Roentgenol 2007;188:105-114.

Reese P, Feldman H, McBride M, et al. Substantial variation in the acceptance of medically complex live kidney donors across US renal transplant centers. Am J Transplant 2008;10:2062-2070.

Rodrigue JR, Pavlakis M, Danovitch GM, et al. Evaluating living kidney donors: relationship types, psychosocial criteria, and consent processes at US transplant programs. Am J Transplant 2007;7:2326-2332.

Roth A, Sonmez T, Unver M, et al. Utilizing list exchange and nondirected donation through 'chain' paired kidney donations. Am J Transplant 2006;6:2694-2705.

Shokeir AA. Open versus laparoscopic live donor nephrectomy: a focus on the safety of donors and the need for a donor registry. J Urol 2007;178:1860-1866.

Singer J, Ettenger R, Gore J. Laparoscopic versus open renal procurement for pediatric recipients of living donor renal transplantation Am J Transplant 2005;5:2514-2518.

Steiner RW, Danovitch GM. The medical evaluation and risk estimation of end-stage renal disease for living kidney donors. In: Steiner RW, ed. Educating, Evaluating, and Selecting living kidney donors. Philadelphia: Kluwer Academic Publishers, 2004:49.

7

Evaluation of Adult Kidney Transplant Candidates

Suphamai Bunnapradist

Gabriel M. Danovitch

Kidney transplantation is the treatment of choice for most suitable end-stage renal disease (ESRD) patients and must be discussed with patients with advancing chronic kidney disease (CKD). The preparation of CKD patients for renal transplantation should start from the time of its recognition and should occur in parallel with efforts to prevent and delay its progression. The improved life expectancy and quality-of-life benefits of transplantation over dialysis therapy have attracted an increasing number of patients to the transplantation option; ideally, patients are evaluated for and undergo transplantation before the initiation of dialysis treatment.

An initial evaluation is followed, if patients are deemed appropriate transplant candidates, by their supervision while awaiting transplantation. Transplant evaluation is aimed not only at assessing the chances of recovery from surgery but also at maximizing short- and long-term survival and assessing the likely impact of transplantation on quality of life. Evaluation of the suitability of kidney transplantation includes medical, surgical, immunologic, and psychosocial issues. The patients' individual risks and benefits of transplantation are discussed so that they can make an informed decision about whether to proceed with transplantation. After candidates are placed on the deceased donor list, a periodic reevaluation is necessary to address new issues that may affect transplant suitability. In this chapter, guidelines are provided for the evaluation of adult kidney transplant candidates. The evaluation should be tailored according to patient-specific conditions. Center expertise should be taken into account when determining which diagnostic studies should be performed.

The process of referral, evaluation, and preparation of patients for transplantation has been extensively reviewed in the professional literature. Several topics critical to the evaluation process are discussed in detail elsewhere in this book. The immunologic evaluation of transplant recipients is discussed in Chapter 3; recommendations for the screening of candidates for infectious disease are discussed in Chapter 11; evaluation of candidates with viral hepatitis and liver disease is discussed in Chapter 12; evaluation of diabetic candidates and the various options for pancreatic transplantation are discussed in Chapter 15; evaluation of children is discussed in Chapter 16; psychiatric

evaluation is discussed in Chapter 17; and psychosocial and financial issues and assessment of compliance are discussed in Chapter 20. Guidelines for the referral and management of patients eligible for solid-organ transplantation have been proposed by the Clinical Practice Committee of the American Society of Transplantation (see Steinman and colleagues in “Selected Readings”). For a detailed algorithmic approach to the evaluation of renal transplant candidates, refer to the clinical practice guidelines developed by the American Society of Transplantation (see Kasiske and associates in “Selected Readings”). For a detailed discussion of the deceased donor transplant waiting list, see Gaston and associates in “Selected Readings.” The proceedings of the Lisbon Conference on the Care of

---

the Kidney Transplant Recipient is a valuable resource of recommendations and references (see Abbud-Filho and colleagues in “Selected Readings”). The Scientific Registry for Transplant Recipients (SRTR) provides annual updates on the status of the kidney transplant waiting list in the United States. The Kidney Disease Improving Global Outcomes (KDIGO) initiative under the leadership of Kasiske and Zeier is developing guidelines on the care of the renal transplant recipient which will become available in late 2009.

PART I. EVALUATION OF TRANSPLANT CANDIDATES BENEFITS OF EARLY REFERRAL

In ideal circumstances, preparation for transplantation begins as soon as progressive CKD is recognized. Chronic renal disease care, care on dialysis, and transplant care are interdependent. Increased cardiovascular risk, which is a major determinant of post-transplantation morbidity and mortality, can be recognized as soon as the serum creatinine level is elevated. The various aspects of the care of patients with CKD are beyond the scope of this text. Better managed patients with CKD, both before and after commencement of chronic dialysis, make better transplant candidates. Patients without the major contraindications to transplantation listed in Table 7.1 should be referred to a transplantation program when they approach stage 4 CKD or a glomerular filtration rate (GFR) less than 30 mL per minute. Patients should understand that referral to a kidney transplantation program does not imply immediate transplantation.

Early referral of patients to nephrologic care during the course of CKD permits better preparation for dialysis and transplantation. Patients who are referred to the care of a nephrologist at least 1 year before commencement of renal replacement therapy are documented to have decreased morbidity and mortality. Unfortunately, 25% to 50% of CKD patients are unaware of their problem until ESRD develops. Transplantation before the commencement of dialysis, called *preemptive transplantation*, has been convincingly shown to improve post-transplantation graft and patient survival. Five- and 10-year graft survival rates are 20% to 30% better in patients who received either no dialysis or less than 6 months of dialysis than for those who received more than 2

years of dialysis. The benefit of preemptive transplantation is likely largely a result of the avoidance of the cardiovascular consequences of long-term dialysis (see Chapter 1).

In the United States, according to the United Network for Organ Sharing (UNOS) deceased donor kidney allocation algorithm in place in 2009 (see

Chapter 4), patients may begin to accrue points on the deceased donor transplant waiting list when the GFR is estimated to be 20 mL per minute or less. However, less than 5% of patients added to the waiting list are predialysis. Because of the long wait anticipated for a deceased donor transplant, preemptive transplantation is infrequent in these patients, unless they are fortunate to be allocated a “zero-mismatch” kidney (see Chapter 4). The great advantage of early referral is that it permits recognition and evaluation of potential living donors and the elective timing of the transplantation so as to avoid dialysis and the necessity for placement of dialysis access. Avoidance of access placement is a great and tempting benefit, but it is one that must be considered carefully. If there is a reasonable doubt that a living donor is available, or that the workup of the donor can be completed expeditiously, it may be wiser to place a permanent access to avoid reliance on temporary access techniques that bring with them added morbidity.

TABLE 7.1 Major Contraindications to Kidney Transplantation

- Recent or metastatic malignancy*
- Untreated current infection
- Severe irreversible extrarenal disease
- Recalcitrant treatment nonadherence
- Psychiatric illness impairing consent and adherence

- Current recreational drug abuse
- Aggressive recurrent native kidney disease
- Limited, irreversible rehabilitative potential
- Primary oxalosis

*See Table 7.2.

Because of the varied course of advanced CKD, it is hard to provide a precise point when referral for transplantation should be made. Patients with diabetic nephropathy typically progress rapidly through the advanced stages of CKD, whereas patients with interstitial nephritis, for example, may progress slowly. Patients with a GFR in the 20s, and patients whose course suggests they will become dialysis dependent in 1 to 2 years, should be referred.

Delays to Referral

All dialysis centers in the United States are mandated to be associated with transplantation centers, and all Medicare patients are legally entitled to referral for transplant evaluation. Unfortunately, there are wide variations in access to transplantation because of delays in the referral process that may tend to disadvantage ethnic minorities and other vulnerable population groups. The large size of the United States and its varied population density also introduce formidable geographic barriers to equality of access. It is the responsibility of nephrologists, dialysis unit staff, transplantation program staff, and the patients themselves to do their utmost to minimize delays and barriers to transplantation.

EVALUATION PROCESS

Patient Education and Consent

Patient education is at the core of the process. Transplant evaluation implies not only the medical assessment of the potential recipient by the transplantation team but also the assessment by the patients of transplant option and its relevance to their well-being. The evaluation process is an opportunity to counsel patients about their ESRD options and to advocate for their welfare. It should not be an obstacle course for patients to pass or fail!

Figure 7.1 illustrates the structure of the evaluation process. All potential transplant candidates should be encouraged to attend an information session, preferably accompanied by family members and friends. At the informational meeting, the risks of the operation and the side effects and risks of immunosuppression should be explained to the patient and family members. The surgical procedure and its complications should also be discussed. The relative benefits of living donor and deceased donor transplantations should be compared and contrasted in the context of the prolonged wait that is anticipated for a deceased donor transplant in the event that a living donor is not available. Graft survival and morbidity statistics from the transplantation program and from national data should be shared with the patient and family members. The nature of rejection should be explained and discussed along with the increased risk for infection, malignancy, and mortality. Patients should be informed about donor risk factors, particularly those associated with deceased

donation (see Chapter 4). Patients should be warned that even a successful transplantation may not last forever and that at some point they may be required to return to dialysis. The importance of compliance with dialysis and dietary prescription while waiting for transplantation and with immunosuppressive therapy after transplantation should be emphasized. The possibility of post-transplantation pregnancy should be discussed with women of childbearing age (see Chapter 10).

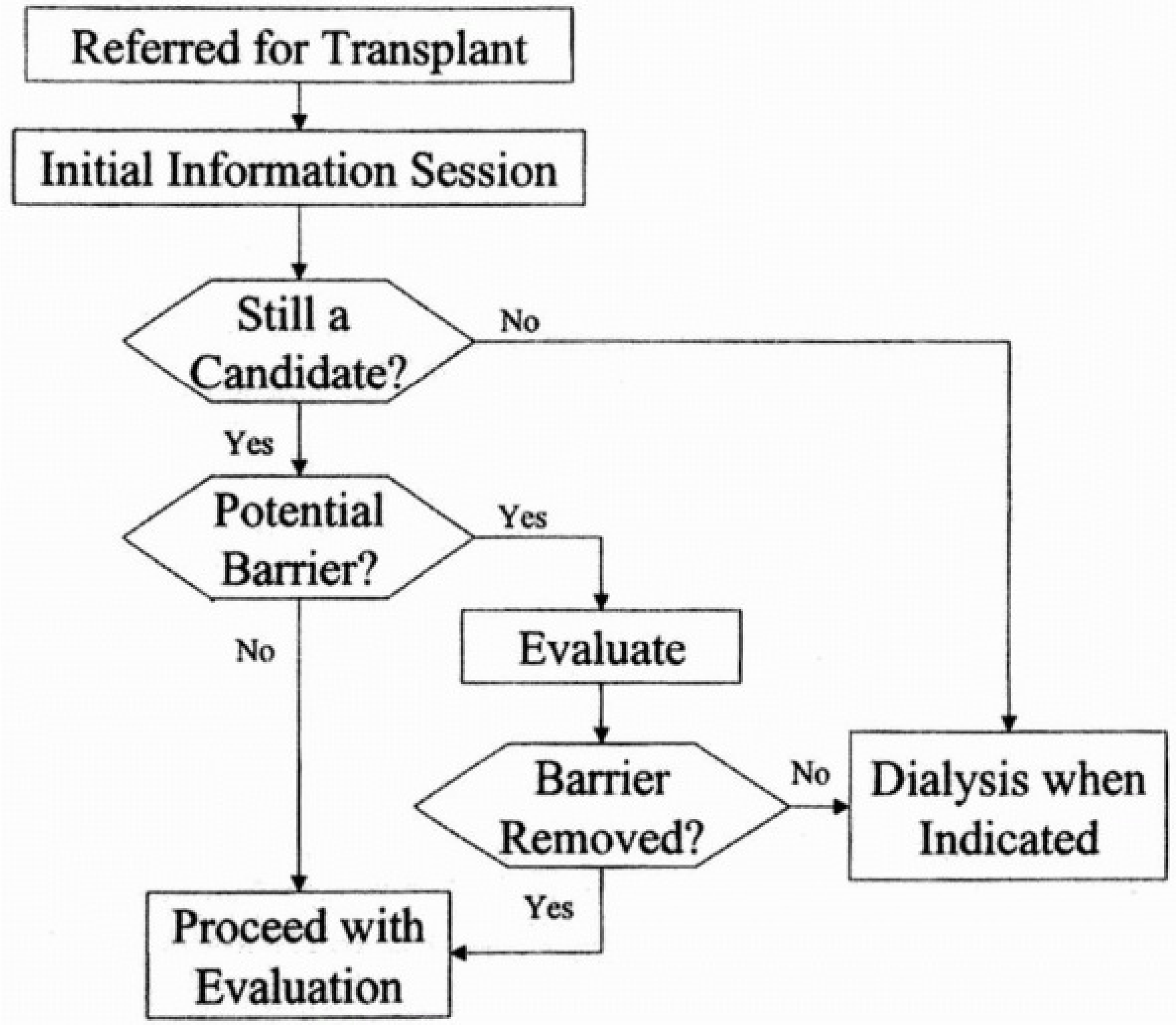


FIGURE 7.1 The renal transplant candidate evaluation process. (From Kasiske BL, Cangro CB, Hariharan S, et al. The evaluation of renal transplant candidates: clinical practice guidelines. Am J Transplant 2001;1[Suppl 2]:1—95, with permission.)

In the United States, the Center for Medicare Services requires that a formal consent process be made available to all patients seeking kidney transplantation. The transplantation program, however, must ensure that the process is not merely a legalistic one and that patient consent truly represents an educated understanding of the options available.

Candidates for Extended Criteria Donor Kidneys

As of 2009, deceased donor kidneys in the United States are categorized as being standard criteria donor kidneys (SCD) and extended criteria donor kidneys (ECD). The precise definition of ECD kidneys, the rationale for their use, and anticipated changes in the categorization of deceased donor kidneys using a donor-risk index are described in Chapter 4. The regulations for the allocation of ECD kidneys mandate that transplant

candidates be informed about the benefits (shortening of waiting time) and risk (impaired long-term graft function) associated with their use. They should sign an informed consent document. A useful guiding principle when counseling patients is to compare the additional risk of accepting an ECD kidney (or a kidney with a high donor risk index) with the risk of remaining on dialysis for a prolonged period while waiting for an SCD kidney (or a kidney with a low donor risk index). Candidates for ECD kidneys are usually 60 years of age or older (younger if they are diabetic or have coronary heart disease); have failing dialysis access; or are particularly intolerant of dialysis. Patients in their 60s who have been on the waitlist

---

for several years may do better to wait for an SCD kidney because they should not have to wait long. Patients going on the list in their 60s may not survive long enough to enjoy an ideal kidney and would be well advised to accept an ECD kidney if they are offered one. The waiting time for SCD and ECD kidneys varies geographically, and patients should be informed of the anticipated waiting time in their geographic area to facilitate an educated decision.

Educational Resources

Potential transplant candidates and their family members should be encouraged to attend formal educational sessions and to obtain further information through available literature, including center-specific outcomes. They should also be familiar with the main features of deceased donor organ allocation policy (Chapter 4). Patient-orientated educational material is available in the United States in printed and electronic form from the American Society of Transplantation (http://www. a-s-t.org), the National Kidney Foundation (http://www.kidney.org), and the United Network for Organ Sharing (UNOS) (http://www.unos.org). The UNOS website also provides detailed information on the performance of individual transplant programs, so-called center-specific data, which can assist patients who have the opportunity to elect the program to which they wish to be referred.

Who Is Not a Transplant Candidate?

The risks and benefits of transplantation should be explained during the initial session because some patients may decide that they do not want to proceed with the evaluation, thus avoiding the need for a costly and time-consuming evaluation. Table 7.1 lists the major contraindications to transplantation. Although some contraindications to transplantation are absolute, many are relative and are determined by local policy and experience. For example, some programs exclude patients who are morbidly obese, or who continue to smoke despite being requested to stop. Attitudes vary about transplantation in the aged or the extent of cardiovascular disease deemed acceptable for transplant candidates. Of the nearly 300,000 patients on dialysis in the United States as of early 2009, only about 25% are on the kidney transplant waiting list (see Chapter 1). Most of the unlisted patients are aged and have

multiple medical morbidities, but many patients are potential candidates who have yet to be referred for transplantation or who have encountered delays in the process. Patients should be presumed to be transplant candidates until shown otherwise. If there is any question regarding a transplant contraindication, the patient should be referred to the transplantation program to make that determination. Patients should be entitled to a second opinion if they find the recommendation of the transplantation program to be unreasonable or unacceptable to them.

Conventional and Innovative Transplantation

Ideally, transplant candidates are unsensitized (see Chapter 3) and have motivated, healthy, ABO-compatible, crossmatch-negative, living donors available to donate to them. If no living donors are available, patients have no option but to wait for a deceased donor transplant, although some patients may elect to shorten their wait by agreeing to accept a lower-quality organ. Patients with hepatitis C may elect to accept a kidney from a deceased donor with hepatitis C (see Chapter 12). In the event that a potential living donor is available but is incompatible by virtue of ABO or histocompatibility differences, another living donor should be evaluated. If a living donor is available but apparently incompatible innovative protocols may be available. ABO-incompatible transplantation and desensitization protocols for histoincompatible donors may be available. Various forms of paired exchange programs designed to facilitate

---

ABO and histocompatible living donation are described in Chapter 6. Figure 7.2 provides an algorithm that can guide patient and program choice and is designed to maximize the opportunities for living donation. Not all of the innovative options described in this algorithm are available at all transplantation programs, although hopefully they will become so for patients who are "difficult to transplant."

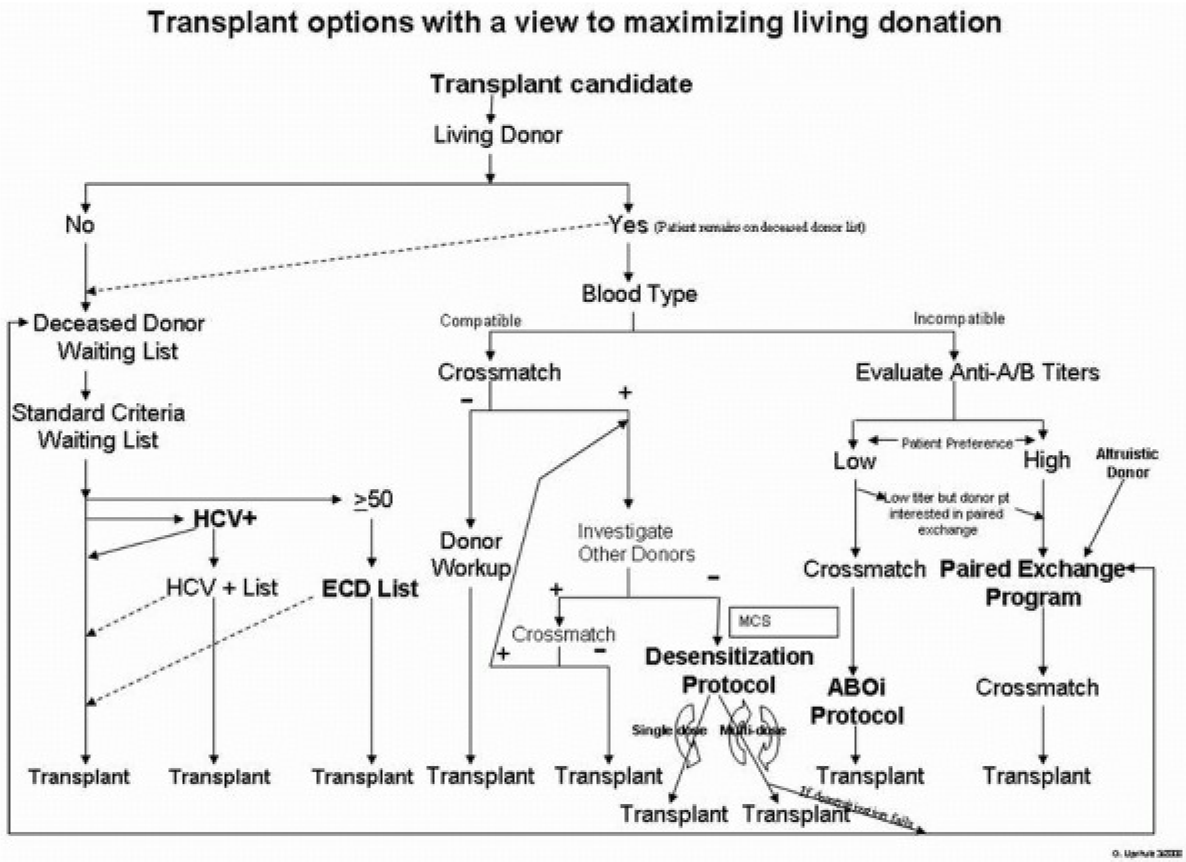


FIGURE 7.2 Transplant options with a view to maximizing living donation.

ROUTINE EVALUATION

History and Physical Examination

A detailed medical history at the time of initial evaluation should be obtained, and efforts should be made to determine the cause of underlying renal disease. Estimation of urine output is important because it may help to determine the significance of the urine output in the early postoperative period and helps to determine the necessity for further urologic evaluation. If a kidney biopsy has been performed, the report should be sought and reviewed. Family history is extremely important because it may provide information regarding the cause of the renal failure and may also allow the physician to initiate discussion regarding living related donation. The evaluation of patients with potentially recurring renal diseases after transplantation is discussed later in the chapter and in Chapter 16.

A detailed cardiovascular history is mandatory for all recipients, and patients should be instructed about symptoms of cardiac disease while awaiting transplantation. Risk factors for coronary artery disease should be sought in the history, including a history of diabetes, smoking, family history of coronary artery disease, and previous cardiac events. Exercise tolerance should be assessed. A history of claudication warrants an evaluation for peripheral vascular disease and may also point toward a higher chance

of ischemic heart disease. A full

physical examination must be performed, including evaluation for evidence of congestive heart failure, carotid artery disease, and peripheral vascular disease. The presence of femoral bruits and poor peripheral pulses may warrant further evaluation of the pelvic vasculature with either a Doppler ultrasound or a magnetic resonance angiogram (see Chapter 13). The presence of strong femoral and peripheral pulses is a valuable indicator to the transplant surgeon that the pelvic vessels will be adequate for the transplant vascular anastomosis (see Chapter 8).

A detailed history of infectious disease should be obtained (see Chapter 11). This should include assessment for possible exposure to tuberculosis, such as history of residence or travel to endemic areas, prior exposure, any prior treatment, and the duration of treatment. Evidence of other possible infections, including hepatitis and endemic fungal infections, should be sought. Male patients older than 40 years should undergo a rectal examination with a digital prostate examination and a prostate-specific antigen estimation. All women should have a Papanicolaou test and a pelvic examination. Women older than 40 years should undergo a mammogram to evaluate for malignancy. All patients older than 50 years and those younger than 50 years with guaiac-positive stools should undergo colonoscopy.

Laboratory Studies

A complete blood count and a chemistry panel should be obtained along with a prothrombin time and partial prothrombin time. Blood should be sent for blood and tissue typing. Patients should be screened for evidence of hepatitis B and C, syphilis, HIV, and cytomegalovirus. A screening purified protein derivative and a screening chest radiograph may be required for certain population to assess for evidence of prior tuberculosis exposure or infection. Patients with a positive skin test or abnormal chest radiograph and those who are allergic to tuberculin and who have risk factors for tuberculosis infection may require preventive therapy with isoniazid (see Chapter 11). A urinalysis and urine culture should be performed on all urinating patients. In the event of proteinuria, a 24-hour urine collection for protein should be obtained, which may reflect the cause of primary kidney disease and be a guide for further management.

EVALUATION OF SPECIFIC TRANSPLANTATION RISK FACTORS RELATED TO ORGAN SYSTEM DISEASE

Cardiovascular Disease

The cardiovascular evaluation of diabetic transplant candidates is discussed in Chapter 15, and evaluation of patients on the transplant waiting list is discussed in Part II of this chapter. Most transplantation teams include a designated cardiologist to assist in the

evaluation of the often complex issues of assessing and managing cardiovascular disease in the CKD population.

Cardiovascular disease is the leading cause of death after renal transplantation. Almost half of deaths in patients with functioning grafts occurring within 30 days after transplantation are due to cardiovascular disease, primarily acute myocardial infarction. Cardiovascular disease is the major cause of longterm mortality and death with graft function, and cardiovascular disease is the major cause of late graft loss (see Chapter 10). All patients with CKD are at high cardiac risk, although for some, the risk is particularly high. Diabetic patients, older patients, patients on dialysis for prolonged periods, and patients with multiple Framingham Study risk factors for coronary artery disease are generally recommended to undergo noninvasive cardiac testing; routine testing of lower-risk asymptomatic patients may not be necessary. Because many dialysis patients are unable to exercise adequately, noninvasive testing usually takes the form of chemical stress echocardiography or scintography. Patients with a positive stress test should proceed to a coronary angiogram. A prior history of ischemic heart disease has been found to be a major risk factor for post-transplantation ischemic events, so that all patients with a history of myocardial infarction or congestive heart failure should undergo cardiac stress testing or, possibly, angiography, even if the stress test is negative. Risk factors associated with post-transplantation ischemic heart disease include age more than 50 years, diabetes, and an abnormal electrocardiogram. Most transplantation programs use noninvasive testing as their initial mode of screening for coronary artery disease, although some prefer to go directly to coronary angiogram. Data are unavailable to test the effectiveness of more expensive screening techniques such as using single photon emission computed tomography (SPECT), positron emission tomography (PET), or electron-beam computed tomography (CT). Both dobutamine stress echocardiogram and dipyridamole sestamibi have similar sensitivities in detecting coronary artery disease in the non-ESRD population. Specific sensitivities and sensitivities for the ESRD population are lacking. Patients who have critical lesions should probably undergo correction with either coronary artery bypass surgery, angioplasty, or stent placement before transplantation.

Calcific aortic stenosis and valvular heart disease are common in transplant candidates, and when they are suspected, it is important to perform an echocardiogram to elicit systolic or diastolic dysfunction because this may have important prognostic implications. Reversible myocardial dysfunction should be treated. Irreversible heart failure should probably preclude renal transplantation unless heart transplantation is also considered. However, many patients with mild to moderate cardiac dysfunction may respond to renal transplantation with an improvement in myocardial function. In many cases, an improvement in the ejection fraction has been documented after transplantation.

Figure 7.3 provides an algorithm that is acceptable to most transplantation programs. These recommendations, however, are made largely on the basis of evidence that is

extrapolated from patients without CKD, and they are not based on the results of prospective clinical trials. It has been suggested that symptom-based evaluation may be as effective as routine cohort-based evaluation, and, whereas cardiac testing may provide prognostic information useful for determining who should be accepted for transplantation, the benefits of such testing for treatment purposes are unproved.

Cerebrovascular and Peripheral Vascular Disease

Successful kidney transplantation has been shown to reduce the risk of vascular disease events involving the cerebral circulation by nearly 50% (See Lentine and colleagues in Selected Readings). Signs and symptoms of cerebrovascular disease in transplant candidates, particularly older candidates, must be evaluated. Dialysis patients experience significantly more ischemic and hemorrhagic strokes and transient ischemic attacks compared with transplanted patients. Risk factors identified for post-transplantation cerebrovascular disease include a history of pretransplantation cerebrovascular disease, age, smoking, diabetes, hypertension, and hyperlipidemia. There is no evidence, however, that routine screening of asymptomatic renal transplant candidates for cerebrovascular disease is beneficial. In the general population, asymptomatic carotid artery stenosis does not correlate with post-transplantation cerebrovascular disease. Patients who have suffered cerebral vascular events and have significant and fixed neurologic deficits may be poor candidates in terms of their perioperative risk and rehabilitative potential. Patients who have had recent transient ischemic attacks or other cerebrovascular events should be assessed by a neurologist. Patients receiving anticonvulsant medications for a seizure disorder should undergo neurologic

assessment to determine whether these medications can be safely discontinued. If anticonvulsants are required, it is preferable to use those that do not have a pharmacologic interaction with the calcineurin inhibitors (see Chapter 5).

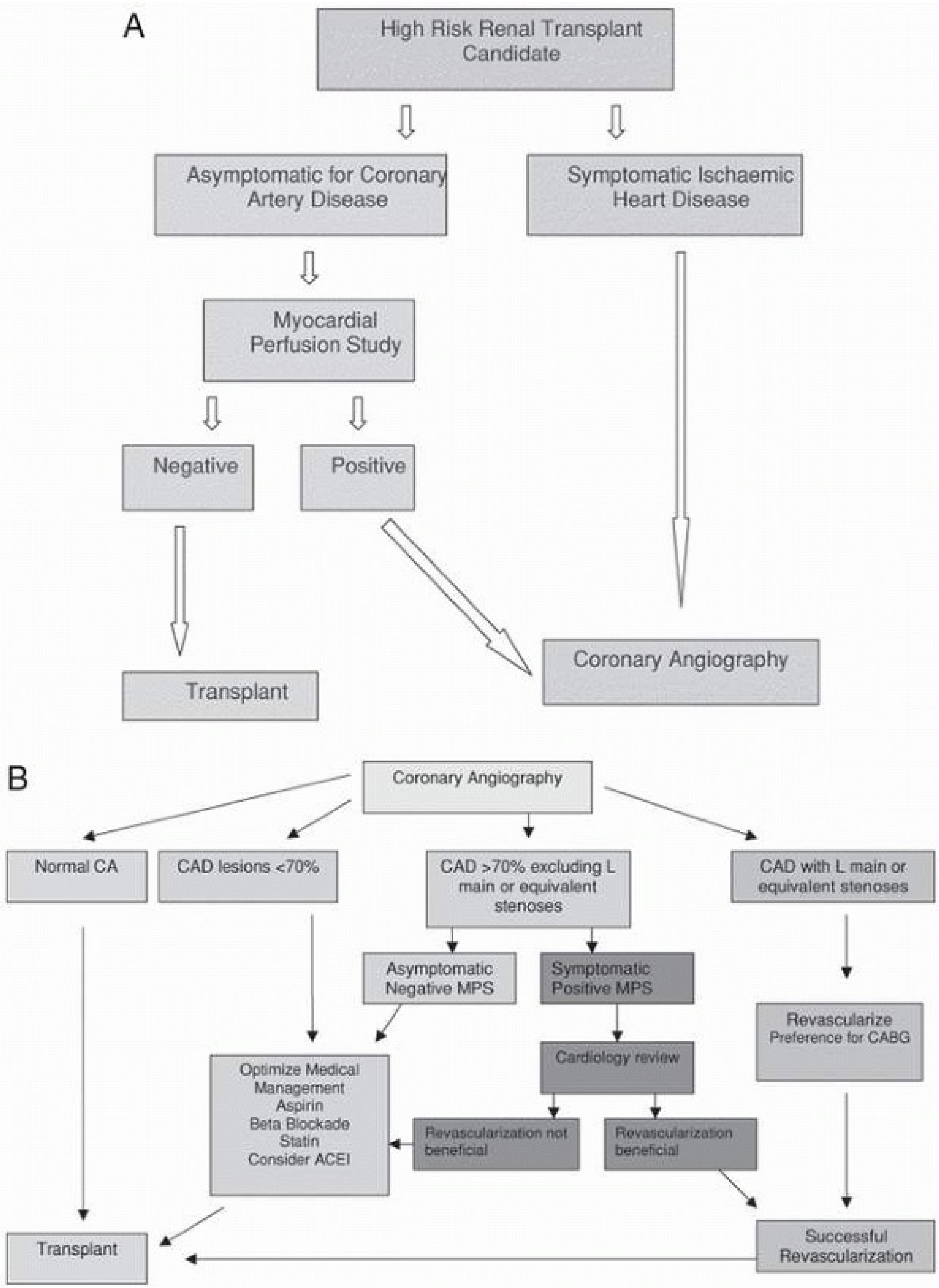


FIGURE 7.3 Proposed algorithm for cardiac evaluation for coronary artery disease in high-risk transplant candidates. (From Pilmore H. Cardiac assessment for renal transplantation. Am J Transplant 2006;6:659—665, with permission.)

Peripheral vascular disease is important both as a cause of allograft ischemia and lower extremity amputation. There is a high incidence of peripheral vascular disease in diabetic recipients. Patients who have undergone lower extremity amputations have a

significantly higher mortality rate within the

ensuing 2 years. Males, diabetics, patients with hypertension, lipid abnormalities, a history of vascular disease elsewhere, and cigarette smoking are at higher risk for peripheral vascular disease patients with diabetes and history of ischemic ulceration in the lower extremity or patients with claudication should, at the very least, have a noninvasive evaluation of the peripheral vasculature. Angiography should be considered if noninvasive studies suggest the presence of large vessel disease. Asymptomatic patients should not be subjected to routine angiography. Patients who have significant aortoiliac disease or have required intra-abdominal reconstructive arterial surgery represent a formidable surgical challenge and transplantation may be contraindicated.

Malignancy

Patients with ESRD have a higher risk for cancer compared with the general population. This relative risk is greatest for patients younger than 35 years of age and decreases gradually with increasing age. CKD patients who required immunosuppressive treatment as part of the therapy of their underlying renal disease or failed prior renal transplantations or required other solid organ transplantations have an additional risk for malignancy. All post-transplantation patients are at increased risk for malignancy (see Chapter 10), and transplant candidates should be forewarned.

Patients who have been successfully treated for a pretransplantation malignancy may be deemed suitable transplant candidates. Much of the data for advice and recommendations regarding transplant candidacy in cancer survivors comes from the Israel Penn International Transplant Tumor Registry, an invaluable resource of information on malignancies and solid organ transplant recipients (http://www.unos.org). Most cancer survivors benefit from a disease-free waiting period, which in most cases is a minimum of 2 years, although in some circumstances, a 5-year waiting period is safer. The precise waiting period, however, should be determined on an individual basis by the type of the tumor, staging of the tumor, and response to therapy. An oncologic consultation may be wise. Broad guidelines for screening and waiting periods for commonly encountered tumors in potential transplant recipients are shown in Table 7.2.

Infections

Pretransplantation screening for infectious disease, together with recommendations for specific infections, is discussed in Chapter 11. Whenever possible, all treatable infections should be eradicated. The presence of chronic infection precludes transplantation and the use of immunosuppressive therapy. Whenever possible, transplant candidates should receive immunization for infections that are prevalent, preferably before the development of ESRD. Osteomyelitis should be treated, and, if necessary, the infected parts should be removed surgically to prepare the patient for

transplantation. Diabetic foot ulcers must be healed before transplantation.

An important change has taken place with respect to the candidacy of patients with HIV infection. Patients with HIV/AIDS were long regarded as inappropriate transplant candidates because of the fear of immunosuppressant-induced opportunistic infection and the anticipation of a short life span. The onset of effective antiviral therapy has radically altered the prognosis of infected patients. Patients who are consistently receiving and tolerating an effective antiviral regimen (with an undetectable viral load and normal T-cell counts) can be considered candidates after completing their evaluation together with education with respect to their high-risk status. The availability and ongoing involvement of an infectious disease consultant familiar with the intricacies of highly active antiretroviral therapy (HAART) regimens is critical when HIV-positive patients undergo transplantation.

TABLE 7.2 Recommendations for Minimum Tumor-Free Waiting Periods for Common Pretransplantation Malignancies*

Tumor Type	Minimal Wait Time
Renal	
Wilms tumor	2 years
Renal cell carcinoma	None (incidental tumors)
	2 years (<5 cm)
	5 years (>5 cm)

Bladder	
In situ	None
Invasive	2 years
Prostate	2 years
Uterus	
Cervix (*in situ*)	None
Cervical invasive	2-5 years
Uterine body	2 years
Breast	2-5 years
Colorectal	2-5 years

Lymphoma	2-5 years
Skin (Local)	
Basal cell	None
Squamous cell	Surveillance
Melanoma	5 years

*The broad recommendations must be individualized based on specific clinical and oncologic information.

Gastrointestinal Disease

Diverticulitis

Diverticulitis is the most frequent cause of colonic perforation in renal transplant recipients. This may be related to the high prevalence of diverticulosis in patients on dialysis, especially patients with adult polycystic kidney disease. Mortality from colonic perforation is high, but the incidence of colonic perforation after renal transplantation has remained stable over many years. It seems reasonable that patients with a history of diverticulitis should be evaluated by a barium enema or a colonoscopy with consideration for resection of extensive disease if symptomatic diverticulitis persists.

Peptic Ulcer Disease

Peptic ulcer was once a frequent and potentially lethal post-transplantation complication that required pretransplantation screening in all patients and surgery in a selected few. With the use of histamine antagonists, antacids, and proton pump inhibitors, the incidence of peptic ulcer disease has declined significantly.

Transplantation is considered safe even in patients with a history of peptic ulcer disease, although active disease should be treated medically before transplantation. The role of Helicobacter pylori infection should be recognized, although routine screening for this organism is generally not recommended.

Cholelithiasis

Patients with a history of cholecystitis and cholelithiasis should undergo pretransplantation evaluation with ultrasound to identify the presence of cholelithiasis and should be considered for cholecystectomy. Some programs recommend cholecystectomy for asymptomatic diabetic patients with cholelithiasis. Cholecystitis may be difficult to recognize after transplantation and can be a source of morbidity.

Pancreatitis

A pretransplantation history of pancreatitis increases the risk for post-transplantation pancreatitis. Post-transplantation pancreatitis has a high morbidity rate. Patients who have suffered episodes of pancreatitis may be more likely to develop post-transplantation diabetes mellitus and should be forewarned. Both prednisone and azathioprine have been implicated in the etiology of pancreatitis. Hyperparathyroidism should be excluded as a possible factor. Other possible contributing factors, such as lipid disturbances, cholelithiasis, and alcohol, should be addressed before transplantation.

Pulmonary Disease

Surgical risks associated with severe lung disease include fluid overload, ventilator dependency, and infection. All patients should be screened with a history, physical evaluation, and chest radiograph to identify lung disease that may increase the risk for major postoperative pulmonary complications. Formal pulmonary function testing may be required to assess surgical risk for patients with known lung disease, patients with signs and symptoms suggesting active lung disease, and patients with sleep apnea. Chronic lung disease may preclude safe general anesthesia, and patients who require supplemental oxygen are generally not transplant candidates. Chronic obstructive lung disease and restrictive lung disease recipients have increased post-transplantation infectious complications and mortality. Patients with evidence of chronic lung disease who continue to smoke must stop before transplantation. They should be directed to smoking cessation programs.

Urologic Evaluation

Ideally, the lower urinary tract should be sterile, continent, and compliant before transplantation. Urinalysis and urine culture should be performed on all urinating

patients. Most patients will have undergone renal imaging studies as part of the evaluation of their underlying renal disease, and the studies themselves or reports thereof should be available at the time of the transplant evaluation. Dialysis patients who have not had an imaging study within the previous 3 years should have a renal ultrasound because of the risk for adenocarcinoma associated with acquired cystic disease.

A voiding cystourethrogram (VCUG) and other urologic procedures are not necessary unless there is a history of bladder dysfunction. Patients with a history of genitourinary abnormalities and individuals younger than 20 years may require a full evaluation including a VCUG, cystoscopy, and urodynamic studies. Patients with bladder dysfunction secondary to neurogenic bladder and those who have chronic infection can often be managed without urinary diversion or bladder augmentation procedures. Self-catheterization may be an acceptable option for some patients, infection being a major complication. Graft implantation into the native bladder is always preferred. Diverted urinary tracts should be undiverted where possible to make the lower urinary tract functional before transplantation. Even a very small bladder may develop normal compliance and capacity after transplantation. Transplantation is possible for patients whose

---

urinary tract has been diverted into an ileal conduit and cannot be undiverted. The rate of urologic complications is high, but the overall patient and graft survival is not different from patients with intact urinary tracts.

Older men frequently have prostatic enlargement and may develop outflow tract obstruction after transplantation. In general, if patients are still passing sufficient volumes of urine, the prostate should be resected preoperatively. Otherwise, the operation should be postponed until after the transplantation has been successfully performed. These patients may require an indwelling bladder catheter or be prepared to self-catheterize until the prostate has been resected.

Patients with adult polycystic kidney (PKD) disease may benefit from unilateral or bilateral nephrectomy to reduce symptomatic bleeding or recurrent infection or for the discomfort suffered because of their massive size. Occasionally polycystic kidneys are so large that they reach deep into the lower abdominal quadrants and may need to be removed to make room for the transplant. Pretransplantation nephrectomy may be indicated for patients with chronic renal infections or infectious renal stones or obstructive uropathy complicated by chronic infections. Patients with uncomplicated recurrent urinary tract infection do not usually require pretransplantation nephrectomy. Bilateral nephrectomy may be recommended in patients with congenic nephrotic syndrome and also in patients with persistent nephrotic syndrome despite optimal medical management. Adenocarcinoma of the native kidneys may manifest after transplantation and is associated with considerable morbidity and mortality. The major indications for pretransplantation native kidney nephrectomy are listed in Table 7.3. If nephrectomy is required, it should be done 6 weeks to 3 months before

transplantation. Occasionally, unilateral transplant nephrectomy is performed at the time of the transplant surgery.

Renal Osteodystrophy and Metabolic Bone Disease

Patients with ESRD suffer from multiple bone disorders, including secondary hyperparathyroidism, osteomalacia, and dialysis-related amyloid bone disease (see Chapter 1). Successful renal transplantation is the best treatment for most cases of osteomalacia and dialysis-related amyloid bone disease. Persistence of hyperparathyroidism after renal transplantation is common. Most renal transplant recipients have elevated parathyroid hormone (PTH) levels at the time of transplantation, and more than 30% of these patients continue to have elevated levels up to 3 years after transplantation. The duration of time on dialysis and the intensity of hyperparathyroidism before transplantation correlate with the

severity of post-transplantation hyperparathyroidism (see Chapter 10). Hypercalcemia is the most common marker of hyperparathyroidism after transplantation. Every attempt should be made to minimize the effect of impaired calcium metabolism, metabolic acidosis, and secondary hyperparathyroidism in the pretransplantation period. Cinacalcet (Sensipar) is an approved and effective therapy, and there is limited experience suggesting that it may be used safely in the post-transplantation period (see Chapter 10). Patients with persistent hyperparathyroidism that is unresponsive to medical therapy may need pretransplantation parathyroidectomy. Older female and diabetic patients should be warned that they may be at an exaggerated risk for osteopenia and pathologic fractures after transplantation.

TABLE 7.3 Indications for Pretransplantation Native Nephrectomy

Chronic renal parenchymal infection
Infected stones
Heavy proteinuria

Intractable hypertension

Polycystic kidney disease*

Acquired renal cystic disease†

Infected reflux‡

* Only when the kidneys are massive, recurrently infected, or bleeding.

† When there is suspicion of adenocarcinoma.

‡ Uninfected reflux does not require nephrectomy.

Hypercoagulable States

There appears to be an increased prevalence of several prothrombotic factors in renal transplant candidates, and thrombophilic patients are at a higher risk for early graft loss. All transplant candidates should have routine coagulation studies performed. Patients who have had a history of thrombosis, including recurrent thrombosis of arteriovenous grafts and fistulas, should have a more extensive coagulation profile performed. This should include screening for activated protein C (APC) resistance, factor V and prothrombin gene mutations, anticardiolipin antibody, lupus anticoagulant, protein C and S, antithrombin III, and homocystine levels. About 6% of Caucasians have APC resistance, usually as a result of heterozygosity for the factor V Leiden mutation. They are prone to thrombotic complications and graft loss. All renal transplant candidates with systemic lupus erythematosus should have antiphospholipid antibodies measured.

Thrombophilia is rarely a contraindication to transplantation, although its recognition should initiate preventive strategies. Perioperative anticoagulation is discussed in Chapter 8. Therapeutic decisions for long-term anticoagulation need to be individualized with respect to the agent used and the length of treatment. Chronic

anticoagulation of dialysis patients with recurrent access thrombosis but without an underlying coagulopathy is often ineffective and should be avoided. Long-standing warfarin administration has been associated with accelerated vascular calcification.

EVALUATION OF RISK FACTORS RELATED TO SPECIFIC PATIENT CHARACTERISTICS

Transplantation in Elderly Patients

The assessment of the transplant candidacy of elderly patients with advanced CKD is challenging. It requires both compassion for the unique predicament of the elderly patient and a dispassionate assessment of the complex issues that transplantation in elderly patients implies.

There is no formal upper age limit at which patients may no longer be accepted for transplantation, although 80 years of age represents a practical biologic limit. About 10% of all patients on the waiting list for renal transplantation in the United States are 65 years of age or older, about 3% are 70 years or older, and this aging trend is continuing. There has been a marked increase in the number of renal transplantations performed in older patients in the past 10 years. Data from the United States show that, as a group, patients 60 years or older who are deemed appropriate transplant candidates and receive a renal transplant survive longer than dialysis patients and have a better survival rate than patients who remain on the transplant waiting list. Similar data are also available for patients older than 70 years, and even for patients older than 75 years. This trend, however, has not been confirmed in older patients in the United Kingdom. Older transplant recipients have an increased risk for death due to cardiovascular disease in the few months after renal transplantation. They also tend to have longer initial hospitalizations but fewer acute rejection episodes because their immune system may be less aggressive. Older patients may be at increased risk for infection and malignancy related to immunosuppression. The metabolism of immunosuppressive drugs may be slowed by aging. The immunosuppressive management of elderly transplant recipients is discussed in Chapter 5.

The possibility of covert coronary artery disease should be routinely evaluated with stress testing, and the need for assessment of cerebrovascular and peripheral vascular disease should be considered. Older patients with significant vascular disease may not be appropriate transplant candidates. Standard malignancy screening recommendations should be applied compulsively in older patients. The assessment of older patients should also take into account their cognitive abilities and their capacity to ambulate and care for themselves in the post-transplantation period. Clearly, there are sprightly patients in their early 70s who are excellent transplant candidates, whereas many patients of this age group would do better to remain on dialysis. Of all the patients older than 65 years on chronic dialysis in the United States, only about 5% are on a

transplant waiting list.

Most of the published data on transplantation in older patients relate to patients older than 60 years. Data on patients older than 70 years is more limited. The available data also tend to relate to the “dry” statistics of patient and graft survival. Most older patients seek improved quality of life in their later years, which they may resent spending on dialysis. Older patients may have unrealistic expectations about their quality of life after transplantation—the transplant will not make them younger! They may also tend to underestimate or discount the risks associated with transplantation in their enthusiasm to be freed from the constraints of chronic dialysis. The waiting time for a deceased donor transplant in the United States is such that older patients may not survive to be allocated a kidney by the standard algorithm, and to benefit from transplantation, they should be encouraged to accept an ECD kidney, as noted previously. Prolonged waiting times dramatically decrease the clinical benefits and economic attractiveness of transplantation. Older patients are often reluctant to accept living donor kidneys from their children, although these kidneys offer them the best chance of meaningful improved survival and quality of life. Even devoted family members may have reservations about living donation for family members with an intrinsically limited life span. These issues must be discussed with older patients and their families with particular care and compassion to optimize the chance of a satisfactory outcome. It should be made clear to older patients that data relating to relative post-transplantation survival come from large database analyses and may not be relevant to individuals, many of whom may be anxious to hear apparently authoritative predictions about their anticipated life expectancy.

Obesity

Malnutrition at the time of dialysis is a strong predictor of short-term and long-term mortality, whereas a high body mass index (BMI) has been associated with reduced mortality among hemodialysis patients, a phenomenon referred to as *reversed epidemiology*. In contrast, obesity is an important risk factor for renal transplant recipients (reversal of reversed epidemiology!) and has been considered by some transplantation centers as an exclusion criteria. About 20% of transplant recipients have a pretransplantation BMI of more than 30 kg/m^2, and this percentage is increasing. Obese renal transplant recipients have a higher risk for delayed graft function and suffer from more surgical

---

complications, including more wound infections. Obesity is also associated with a prolonged post-transplantation hospital stay, increased cost of transplantation, and a higher incidence of post-transplantation diabetes and cardiovascular disease (see Chapter 10). Obese recipients of combined kidney-pancreas transplantation have also reported decreased pancreas and renal graft survival rates.

Some authorities have recommended excluding patients with a BMI greater than 35

kg/m^2 from transplantation, although the available patient and graft survival data in this group are not significantly less than for nonobese patients. BMI alone can be a misleading predictor of risk, and fat distribution and muscle mass should also be considered. Abdominal obesity is a particular concern both in terms of surgical risk and as a marker for the metabolic syndrome. Special attention should be given to the cardiac evaluation of obese renal transplant candidates. Obese elderly patients and those with concomitant coronary heart disease may have a worse prognosis, and these patients may be better served by remaining on dialysis. It is tempting and may seem intuitively appropriate to recommend, or even demand, weight loss in obese transplant candidates. Such recommendations, however, may put dialysis patients at risk and have not been proved to improve outcome. It is better to individualize transplant recommendations regarding weight loss rather than make broad exclusionary rules base on an arbitrary BMI or demands for BMI reduction. If weight loss is deemed necessary, it should be supervised by a trained dietitian (see Chapter 19). There is limited experience in bariatric surgery for transplant candidates.

Highly Sensitized Patients

The immunologic challenge faced by highly sensitized patients is discussed in Chapter 3. About 40% of patients awaiting deceased donor transplants in the United States have high levels of preformed cytotoxic antibodies that may prevent them from receiving a kidney or prolong their wait considerably. Cytotoxic antibodies result from failed prior transplants, multiple pregnancies, and multiple blood transfusions. Attempts have been made to reduce the antibody levels by infusion of intravenous immune globulin (IVIG), plasma exchange with cyclophosphamide and immunoabsorption, and rituximab (see Chapter 5). Use of IVIG with rituximab in these circumstances appears to be the most promising (see Vo and colleagues in “Selected Readings”). Patients with high levels of antibodies should be warned of the probability of a prolonged wait for a kidney. The widespread use of erythropoietin in dialysis patients may serve to lower the level of preformed antibodies by minimizing blood transfusion requirements. The innovative transplantation techniques discussed previously (Fig. 7.2) may be a way to overcome the barriers imposed by sensitization.

Previously Transplanted Candidates

The fate of second and multiple transplantations is dependent to a considerable extent on the rate and etiology of the prior transplant loss. Patients who lost kidneys because of surgical complications or have kidneys that functioned for more than a year have a prognosis that is not significantly different from patients with primary transplants. If the primary transplant is lost to early rejection, the prognosis for another transplant is impaired, and the patient will do best with a highly matched cadaveric transplant or a two-haplotype—matched living related transplant if a suitable donor is available. Patients must be made aware of their impaired prognosis.

The process of evaluating a patient for a repeat transplantation is the same as for a primary transplantation. For patients whose first transplant life was prolonged, special attention should be paid to the possibility of covert coronary artery disease or malignancy. Patients with a failing transplant should be referred early for retransplantation in the hope of avoiding the need to return to dialysis. Multiple transplanted patients are at an increased risk for immunosuppressant-related malignancy and infection and should be forewarned. Patients whose first deceased donor transplant was lost within the first three months, whether for technical or other reasons, are able to maintain their original waiting time on the UNOS waiting list (See Chapter 4).

Candidates for Double Organ Transplants

Patients with end-stage liver disease (ESLD) who are candidates for orthotopic liver transplantation (OLT) frequently have impaired renal function as a result of hepatorenal syndrome, prerenal dysfunction, acute tubular necrosis, or nephrotoxicity. In most cases, renal function will improve following successful OLT despite what is often a prolonged period of dialysis dependence. Concomitant renal transplantation is therefore not indicated when it is anticipated that native renal function will improve.

Irreversible renal dysfunction may accompany ESLD; in these cases, it is logical to consider a combined procedure. The addition of a kidney transplant adds relatively little to the considerable morbidity of an OLT, but a well-functioning kidney may facilitate post-transplantation management. The indications for combined kidney-liver transplantation are discussed further in Chapter 12 and are listed in Table 12.3.

Experience with combined heart-kidney transplantation is more limited, but many of these procedures have been performed successfully. The same principles regarding reversibility of renal dysfunction apply.

RELEVANCE OF THE ETIOLOGY OF RENAL DISEASE TO THE TRANSPLANT EVALUATION

The cause of CKD is important for prognosticating transplant outcome. This information may also be critical in selecting a suitable living donor for transplantation. The risk for recurrence of the native kidney disease in the transplant is summarized in Table 7.4, which can be used as a guide to counsel patients. The effects of recurrent renal disease on the post-transplantation course are discussed in Chapter 10.

TABLE 7.4 Risk for Recurrent Disease After Renal Transplantation

Recurrent Disease	Risk (%)
Focal and segmental glomerulosclerosis	30-50
Immunoglobulin A nephropathy	40-60
MPGN-I	30-50
MPGN-II	80-100
Membranous nephropathy	10-30
Diabetic nephropathy	80-100 (by histology)
HUS/TTP	50-75
Oxalosis	80-100
Wegener disease	<20
Fabry disease	<5

Systemic lupus erythematosus	3-10

HUS, hemolytic uremic syndrome; MPGN, membranoproliferative glomerulonephritis; TTP, thrombotic thrombocytopenic purpura.

Diabetes Mellitus

The special considerations related to the evaluation of diabetic transplant candidates, who account for about 40% of the ESRD population in the United States, are considered in Chapter 15. Diabetic transplant recipients can develop histologic features of diabetic nephropathy as early as 3 years after transplantation. However, patients should be informed that recurrent diabetic nephropathy is an uncommon cause of graft failure, and its possibility should not be used as the sole reason to seek the more complex simultaneous kidney-pancreas transplantation. Optimal management of diabetes while on dialysis is a critical factor in the prevention of post-transplantation diabetic complications. Diabetic education should be reinforced at the time of transplant evaluation.

Focal and Segmental Glomerulosclerosis

This discussion relates to primary focal and segmental glomerulosclerosis (FSGS). FSGS that is secondary to reflux nephropathy and obesity, for example, does not recur after transplantation. Evidence of focal sclerosis is often found on histologic evaluation of patients with hypertensive renal disease and other causes of CKD and should be differentiated from the primary disorder. Presumably as a result of an unidentified serum factor that affects the permeability of the glomerular basement membrane (GBM), transplant candidates with primary FSGS have a high incidence of recurrence after transplantation, reported between 20% and 40%. The odds of recurrence are increased in patients who are younger (see Chapter 16), those who had a rapid progression to ESRD, those with the collapsing variant, and those whose initial biopsy showed mesangial hypertrophy. The strongest predictor of recurrence is a history of recurrence in a previous transplant. Patients should be forewarned of the possibility of recurrence. If a living donor is being considered, both the transplant candidate and the potential donor should be aware of the risk for graft loss from recurrent FSGS. Plasma exchange before transplantation and in the early post-transplantation period has been suggested to reduce the risk for recurrent disease, but its effectiveness has been difficult to prove.

Some patients with FSGS continue to have heavy proteinuria while on dialysis. In these cases, native kidney nephrectomy may be indicated both for nutritional consideration and because persistent massive native kidney proteinuria makes the evaluation of post-transplantation proteinuria very difficult. Post-transplantation management and prevention of recurrent FSGS is discussed in Chapter 10, and also in Chapter 16 because recurrent FSGS is a particular problem in children. Patients who have lost a prior transplant to recurrent FSGS are a high risk for re-recurrence, and this is an important consideration in assessing their candidacy for a repeat transplantation. Some programs avoid living donor transplantation in these circumstances.

Recurrent Glomerulonephritis

The recurrence rates of the most common primary glomerulopathies are shown in Table 7.4 and are also discussed in Chapter 16. Recurrent disease estimates are imprecise because only about 20% of CKD patients have a specific histologic diagnosis at the time of presentation for transplant evaluation. The rate of recurrence of the glomerulopathies continues to increase with longer duration of follow-up of after transplantation and may be more common in recipients of living related transplants. Evidence of histologic recurrence of immunoglobulin A (IgA) nephropathy is common, although graft loss due to recurrent IgA nephropathy is uncommon and has been reported in about 10% of patients. Recurrent IgA nephropathy in a prior transplant is generally not a contraindication for repeat transplantation, and re-recurrence is not inevitable. IgA nephropathy may be familial in some cases, and donors should be carefully screened (see Chapter 6).

Thrombotic Thrombocytopenic Purpura

There is a high rate of recurrence of the nondiarrheal form of thrombotic thrombocytopenic purpura (TTP) and nearly 50% graft failure from that recurrence (see Chapter 16). Older age at onset, a shorter interval between onset of ESRD and transplantation, the use of living donors, and the use of calcineurin inhibitors have all been associated with recurrence. Both the calcineurin inhibitor drugs may induce a TTP-like syndrome (see Chapter 5), although its severity is typically less than in the recurrent form. Patients and living donors should be counseled regarding risks for recurrence in patients with a history of TTP, and consideration should be given to a calcineurin inhibitor—free regimens. Patients should be advised to avoid oral contraceptives.

Systemic Lupus Erythematosus and Vasculitis

Recurrence of SLE can occasionally lead to graft failure. Clinical activity of SLE should be quiescent before transplantation. The patient should not require cytotoxic agents or more than 10 mg of prednisone before transplantation to maintain quiescence.

Clinically active SLE typically improves with the development of chronic renal failure, but may not do so in some patients, particularly African American women. Some patients are clinically quiescent but maintain persistently abnormal levels of serologic markers of disease activity while on dialysis. It is the degree of clinical activity that should determine transplant candidacy.

Patients with antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis are at risk for recurrent disease; however, pretransplantation ANCA levels are not predictive of recurrence in asymptomatic patients. Successful transplantation has been reported in active disease, but it will probably be wise to wait until the disease is quiescent before transplantation.

Patients who are heavily immunosuppressed during the course of their native kidney disease may be at increased risk for post-transplantation opportunistic infections and lymphoma. The risk for avascular necrosis is higher in patients with SLE, most of whom have received high doses of corticosteroids during the course of their illness.

Oxalosis and Oxaluria

Primary oxalosis is a rare cause of renal failure. It is an autosomal recessive disorder due to deficiency of the hepatic enzyme alanine glyoxylate aminotransferase. The presence of this enzyme leads to increased urinary secretion of calcium oxalate and nephrocalcinosis, which leads to renal failure. Accumulation of oxalate occurs throughout the body. Failure of the graft usually occurs after transplantation with rapid deposition of oxalate in the graft. Failure of the graft usually occurs despite intensive therapy with perioperative intensive dialysis and oral phosphates, which are designed to minimize oxalate deposition. All reduce renal calcium oxalate deposition, whereas pyridoxine is a coenzyme that functions in conversion of glyoxylate to glycine. Combined liver and kidney transplantation is the best option for patients with primary oxalosis (see Chapters 12 and 16). The transplanted liver provides the absent enzyme. Because the usual parameters of hepatic function are normal in these patients, they may require a prolonged wait for a transplant in countries where the severity of hepatic dysfunction is the major determinant of liver allocation. It has been suggested that isolated kidney transplantation is a reasonable first option for patients with oxalosis as long as the precautions listed earlier are adhered to rigorously and patients are adequately warned of the recurrence risk.

Secondary hyperoxaluria is most commonly of intestinal origin and may also lead to recurrence in the allograft. Patients have usually suffered from inflammatory bowel disease or morbid obesity. If the underlying defect is reversible (e.g., intestinal bypass for obesity), consideration should be given to surgical reversal before transplantation. In urinating patients, the 24-hour excretion of oxalate should be checked to help assess the risk for recurrent oxalosis.

Fabry Disease

Fabry disease is due to a deficiency of a-galactosidase enzyme, which results in accumulation of glycosphingolipid in the kidney and other organs. It was initially hoped that kidney transplantation would provide enough enzyme to prevent disease progression, but this has not proved to be the case, and Fabry disease may recur and progress in the transplanted kidney. Recurrence is slow, and death is usually caused from sepsis and other systemic complications. Renal transplantation is the treatment of choice for patients with Fabry disease who do not have severe systemic disease. Fabrazyme is a newly available recombinant form of the deficient human enzyme, which may have a major beneficial impact on the course of the disease.

Alport Syndrome

Patients with Alport syndrome have a genetic abnormality of type 4 collagen that is X-linked in 80% of patients. Autosomal recessive (15%) and autosomal dominant (5%) forms also occur. The introduction of normal collagen in the basal membrane of the transplanted kidney may induce antibody formation to donor kidney collagen found in the GBM. The precise incidence of anti-GBM antibody formation is unknown, although clinically significant anti-GBM nephritis is rare. Graft survival is not impaired in patients with Alport syndrome. Patients should be warned that there is a potential to develop clinically significant anti-GBM disease, which may occur in a subsequent transplant graft. The presence of inherited kidney disease always requires intensive family screening before consideration of living related donation.

Sickle Cell Disease

Sickle cell disease often leads to ESRD, probably by causing chronic intestinal fibrosis, but FSGS and nephrotic syndrome also do occur. Short-term patient and graft survival rates are not different from those in patients without sickle cell disease; however, long-term mortality is increased about 2.5-fold. There is an increased incidence of severe, and potentially lethal, sickling crisis after transplantation, presumably related to the improving hematocrit. Exchange transfusions may be an effective treatment. There is a trend toward improved survival for transplanted patients with sickle cell disease compared with sickle cell disease patients who remain on the waiting list. Renal transplantation appears to be the treatment of choice for patients without severe systemic complications.

Amyloidosis and Plasma Cell Dyscrasias

Patients with primary amyloidosis are high-risk transplant candidates. Their mortality rate after transplantation has been reported to be as high as 50% at 1 year. Infectious and cardiac complications are common. In general, patients with primary amyloidosis should be discouraged from renal transplantation, although some patients without

severe extrarenal disease may be considered acceptable candidates. Patients with secondary amyloidosis are more likely to be acceptable candidates. An echocardiogram should be performed to assess the extent of myocardial infiltration. The subgroup of patients with amyloidosis complicating familial Mediterranean fever (FMF) may not tolerate the combination of colchicine and cyclosporine therapy as a consequence of systemic and gastrointestinal symptoms. Recurrence of amyloid deposition in the allograft is

common. Light-chain disease also has a high rate of recurrence and associated morbidity, although some patients have been reported to do well for long periods after transplantation.

The pretransplantation evaluation of all patients older than 60 years should include plasma immunoelectrophoresis to screen for paraproteins. The rate of conversion from benign monoclonal gammopathy to frank multiple myeloma is about 1% per year. If a benign monoclonal gammopathy of long-standing duration is known, transplantation can be performed. Transplantation should be delayed for at least 12 months in other cases to exclude the development of myeloma or microglobulin anemia. If, after follow-up, there is no evidence of progression to myeloma, it is reasonable to progress with transplantation. Patients should be instructed about higher morbidity risk in the post-transplantation period. Occasional cases of successful transplantation for patients with myeloma have been reported, although this disease is usually regarded as a contraindication to transplantation. Patients with myeloma who have been successfully treated by bone marrow transplantation may be considered to be transplant candidates. Extraordinary cases have been reported of simultaneous bone marrow transplantation and kidney transplantation from the same fully matched living donor.

Polycystic Kidney Disease

Patients with PKD are excellent potential transplant candidates. The graft and patient survival rates are not different from those in other low-risk groups. The necessity for pretransplantation or post-transplantation nephrectomy was discussed previously. There may be an increased risk for gastrointestinal complications after transplantation, usually related to diverticular disease. Patients with headaches or other symptoms of the central nervous system or with a family history of aneurysm should undergo noninvasive screening for cerebral aneurysm. The possibility of living related donation in families with polycystic kidney is discussed in Chapter 6.

PART II: MANAGEMENT OF THE WAITING LIST FOR A DECEASED DONOR TRANSPLANT

As of early 2009, close to 85,000 patients were listed on the waiting list for a deceased donor kidney in the United States. This number has been steadily increasing and is likely to continue to increase. The overall number, however, includes candidates who

have been placed on the list in an “inactive” status (see Chapter 4), typically because their evaluation is incomplete or new issues have developed that contraindicate transplantation, presumably on a temporary basis. The number of “active” candidates has remained stable at about 50,000 between 2005 and 2009. After patients are placed on the transplant waiting list, they are likely to face a prolonged wait until a kidney becomes available to them. The mortality rate on the waiting list has been estimated to 6% per annum overall and even higher in diabetics. The estimated mortality rate, however, relates to the whole list that includes both active and inactive candidates. It is likely that many of the deaths occur in inactive candidates, but clearly premature deaths also occur in active candidates. In addition to the risk for death associated with a prolonged wait and the associated impact on morbidity and life quality, a prolonged wait for a transplant has a major impact on post-transplantation outcome, likely because of the progression of vascular comorbidity while on dialysis.

During the long years patients spend waiting, their health, particularly their vascular health, may deteriorate, and the conclusions drawn from the initial evaluation may no longer apply. For this reason, it is critical that there be ongoing communication between dialysis units, patients, and transplantation programs regarding health and demographic issues that may be relevant to the transplant candidacy. All dialysis patients, but particularly patients awaiting transplantation, should receive optimal care according to accepted guidelines during their prolonged wait for a transplant to minimize post-transplantation morbidity. Performance of preventive health measures recommended in the general population (e.g., mammography, lower endoscopy) should be decided on an individual basis because the risk-to-benefit ratio of such testing may be less favorable in a population whose intrinsic life span is limited.

TABLE 7.5 Recommendations for Cardiac Surveillance of Waitlisted Patients

Initial Evaluation Negative
Diabetic ESRD—annually
Nondiabetic “high risk”*—biannually

“Low-risk”—every 3 years

Initial Evaluation Positive

No prior revascularization—annually

Prior percutaneous coronary intervention—annually

Post—coronary artery bypass: successful†—every 3 years, then annually;

incomplete—annually

Asymptomatic moderate or worse aortic stenosis—echocardiogram annually

* High-risk (more than 20% per 10 years cardiovascular event rate risk) according to Framingham data includes those with two or more “traditional” risk factors, a known history of coronary disease, left ventricular ejection fraction < 40%, or peripheral vascular disease.

†Complete revascularization of all target vessels.

(From Gaston RS, Danovitch GM, Adams PL, et al. The report of a national conference on the wait list for kidney transplantation. Am J Transplant 2003;3:775—785, with permission.)

Most transplantation programs attempt to reassess each patient's candidacy on an annual basis. In addition to updating the patient's medical status, this reassessment also provides an opportunity to review the availability of living donors and to educate patients with regard to changes in allocation rules that may be relevant to them.

Patients and family members who may have been reluctant to consider living donation when the transplant evaluation process began may wish to reconsider after a prolonged period on dialysis. For older patients, the advantages and disadvantages of receiving an ECD kidney should be addressed. There is widespread agreement among transplantation programs that repeated cardiovascular surveillance is required for many patients while awaiting a transplant and that, in high-risk patients, this surveillance should be more intense. A suggested protocol for this follow-up is shown in Table 7.5. For recommendations regarding repetition of screening tests for infectious diseases and HLA antibody reactivity, refer to Gaston and associates in “Selected Readings.”

RELEVANCE OF THE ALLOCATION ALGORITHM TO THE PREDICTABILITY OF TRANSPLANTATION

Deceased donor transplantation is unique among surgical procedures in that it is an urgent procedure performed in an elective population. The inclusion of HLA matching in deceased donor kidney allocation algorithms makes it difficult to anticipate with any degree of accuracy when a given patient will be called for his or her long-awaited transplant. This unpredictability has presented

---

transplantation programs with the formidable challenge of attempting to ensure that large numbers of patients, most of whom are not under their direct care, are medically cleared for transplantation at all times. A consequence of their not being cleared is that transplantations may need to be cancelled, resulting in prolongation of ischemic injury to the allograft, or a decision may be made to proceed with the transplantation, placing the patient at unnecessary or unrecognized risk. Unpredictability has, in fact, been implicated as a cause of death in the first post-transplantation year, particularly in older patients, diabetic patients, and patients with vascular disease.

The greater the number of points for HLA matching in the allocation algorithm, the greater is the degree of unpredictability. In the allocation algorithm that was in place in the United States up until May 2003, seven points were given to matching, thus exposing the patients on the top 7 years of the list to the likelihood of being allocated a kidney. As of 2009, two points are given for matching, so that it is the patients on the

top 2 years of the list who are likely to be allocated a kidney. The impact of the anticipated new allocation algorithm on predictability is discussed in Chapter 4. For kidneys allocated based on waiting time alone, it is easy to predict which patient in each blood group category is likely to be allocated a kidney and to ensure that they are ready to proceed safely.

In the United States, the policy on national sharing of zero-mismatched kidneys that remains in place as of early 2009 means that, in principle, any patient can be offered a kidney at any time because the allocation of these kidneys takes priority over other determinants of allocation. Close to 20% of kidneys are allocated in this fashion. In practice, close to 80% of zero-mismatched kidneys are allocated within the first 2 years after patients are placed on the list. This is because recipients with common HLA types rapidly receive kidneys from donors with common HLA types. Patients who have undergone a thorough workup at the time of listing should still be prepared to accept these kidney offers. Changes are anticipated in the allocation algorithm in the United States (see Chapter 4), and different allocation algorithms are used in different countries and regions. Transplantation programs need to ensure that their policies regarding the management of the waiting list are attuned to applicable local allocation algorithms.

Selected Readings

Abbud-Filho M, Adams PL, Alberu J, et al. A report of the Lisbon Conference on the Care of the Kidney Transplant Recipient. Transplantation 2007;83(8 Suppl):S1.

Ashby V, Kalbfliesch J, Wolfe RA, et al. Geographical variability in access to primary kidney transplantation in the United States, 1996—2005. Am J Transplant 2007;7(Suppl 1):1412—1423.

Casingal V, Glumac E, Tan M, et al. Death on the kidney transplant waiting list: good candidates or not? Am J Transplant 2006;6:1953—1956.

Choy BY, Chan TM, Lai KN. Recurrent glomerulonephritis after kidney transplantation. Am J Transplant 2006;6:2535.

Danovitch GM. A kidney for all ages. Am J Transplant 2006;6:1267—1268.

Danovitch GM, Hariharan S, Pirsch JD, et al. Management of the waiting list for cadaveric kidney transplants: report of a survey and recommendations by the Clinical Practice Guidelines Committee of the American Society of Transplantation. J Am Soc Nephrol 2002;13:528.

Gaston RS, Danovitch GM, Adams PL, et al. The report of a national conference on the wait list for kidney transplantation. Am J Transplant 2003;3:775.

Gore JL, Pham PT, Danovitch GM, et al. Obesity and outcome following renal transplantation. Am J Transplant 2006;6:357.

Hickson L, Gera M, Amer H, et al. Kidney transplantation for primary segmental glomerulosclerosis:Outcomes and response to therapy for recurrence. Transplantation 2009;87:1232—1239.

Kasiske BL, Cangro CB, Hariharan S, et al. The evaluation of renal transplant candidates: clinical practice guidelines. Am J Transplant 2001;1[Suppl 2]:1—95.

Lentine K, Rocca Rey L, Kolli S, et al. Variations in the risk for cerebrovascular events after kidney transplant compared with experience on the waiting list and after graft failure. Clin J Am Soc Nephro 2008;3:1090—1101.

Marcen R. Cardiovascular risk factors in renal transplantation—current controversies. Nephrol Dial Transplant 2006;21(Suppl 3):3.

Modanlou K, Muthyala U, Xiao H, et al. Bariatric surgery among kidney transplant candidates and recipients: Anslysis of the United States Renal Data System and literature review. Transplantation 2009;87:1167—1173.

Montgomery RA, Hardy MA, Jordan SC, et al. Consensus opinion from the antibody working group on the diagnosis, reporting, and risk assessment for antibody-mediated rejection and desensitization protocols. Transplantation 2004;78:181.

Patel R, Mark PB, Johnston N, et al. Prognostive value of cardivascular screening in potential renal transplant recipients: a single center prospective observational study. Am J Transplant 2008;8:1673—1683.

Pilmore H.Cardiac assessment for renal transplantation. Am J Transplant 2006:6:659—665.

Shah T, Kasravi A, Huang E, et al. Risk factors for development of new-onset diabetes mellitus after kidney transplantation. Transplantation 2006;82:1673.

Steinman T, Becker B, Frost A, et al. Guidelines for the referral and management of patients eligible for solid organ transplantation. Transplantation 2001;71:1184—1124.

Vo A, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med 2008:359;242—251.

Witczak BJ, Hartmann A, Jenssen T, Foss A, Endresen K. Routine coronary angiography in diabetic nephropathy patients before transplantation. Am J Transplant 2006;6:2403.

8

The Transplant Operation and Its Surgical Complications

Jeffrey L. Veale

Jennifer S. Singer

H. Albin Gritsch

Kidney transplantation is an “elective” surgical procedure performed in patients who have undergone careful preoperative assessment and preparation. Chronic dialysis enables patients to be maintained in optimal condition and provides time to address potentially complicating medical and surgical issues. In this respect, kidney transplantation differs from heart, lung, or liver transplantation, in which the condition of the patient is often deteriorating rapidly in the pretransplantation period.

TRANSPLANTATION OPERATION

Immediate Preoperative Preparations

If transplant candidates have been well prepared (see chapter 7), it is rarely necessary to call off surgery because of last-minute findings. Occasionally, cancellation of surgery is required because of recent events, such as new onset of chest pain or cardiographic changes, diabetic foot ulcers, peritonitis, pneumonia, or gastrointestinal bleeding.

The decision to dialyze a patient before transplantation depends on the timing of the previous dialysis, clinical assessment of volume status, and serum electrolyte levels, particularly potassium. Pretransplantation dialysis is associated with an increased incidence of delayed graft function. Because of the danger of intraoperative or postoperative hyperkalemia in oliguric patients, it is wise to dialyze patients with a serum potassium level of more than 5.5 mEq/L. In welldialyzed patients, preoperative dialysis for fluid removal is usually unnecessary. If fluid is removed, it should be done with care to maintain the patient at or somewhat above dry weight to facilitate postoperative diuresis. If time constraints demand it, a brief preoperative dialysis lasting 1 to 2 hours may be all that is necessary to reduce potassium levels and to optimize the hemodynamic status.

Operative Technique

Because all kidney transplant recipients receive immunosuppressive drugs, and because many are anemic or malnourished at the time of surgery, wound healing is potentially compromised. Meticulous surgical technique, attention to detail, strict aseptic technique, and perfect hemostasis are essential. Drains should be closed systems and should be removed as quickly as possible.

Incision

After the administration of prophylactic antibiotics, a lower abdominal *Gibson* incision is made (Fig. 8.1). It can be extended into the flank, or as high as the tip of the 12th rib, if more exposure is needed. In a first transplantation, the incision site may be in either lower quadrant. There are different approaches to the decision regarding which side to use. One approach is to always use the right side, regardless of the side of origin of the donor kidney, because the accessibility of the iliac vein makes the operation easier than on

the left side. Another approach is to use the side contralateral to the side of the donor kidney; that is, a right kidney is put on the left side, and vice versa. This technique was used when the hypogastric artery was routinely used for the anastomosis because the vessels lie in a convenient position and the renal pelvis is always anterior, making it accessible if ureteral repair is needed. The third approach is to use the side ipsilateral to the donor kidney; that is, a right kidney is put on the right side, and vice versa. This choice is best when the external iliac artery is used for the arterial anastomosis. The vessels then lie without kinking when the kidney is placed in position. In repeat transplantations, the side opposite the original transplant is generally used. In further transplants, the decision regarding where to place the kidney is more complex; a transabdominal incision may be necessary, and more proximal vessels may be used. In patients with type 1 diabetes who may be eventual candidates for pancreas transplantation, the kidney is preferentially placed in the left iliac fossa to facilitate a possible pancreas transplantation on the right side (see Chapter 15).

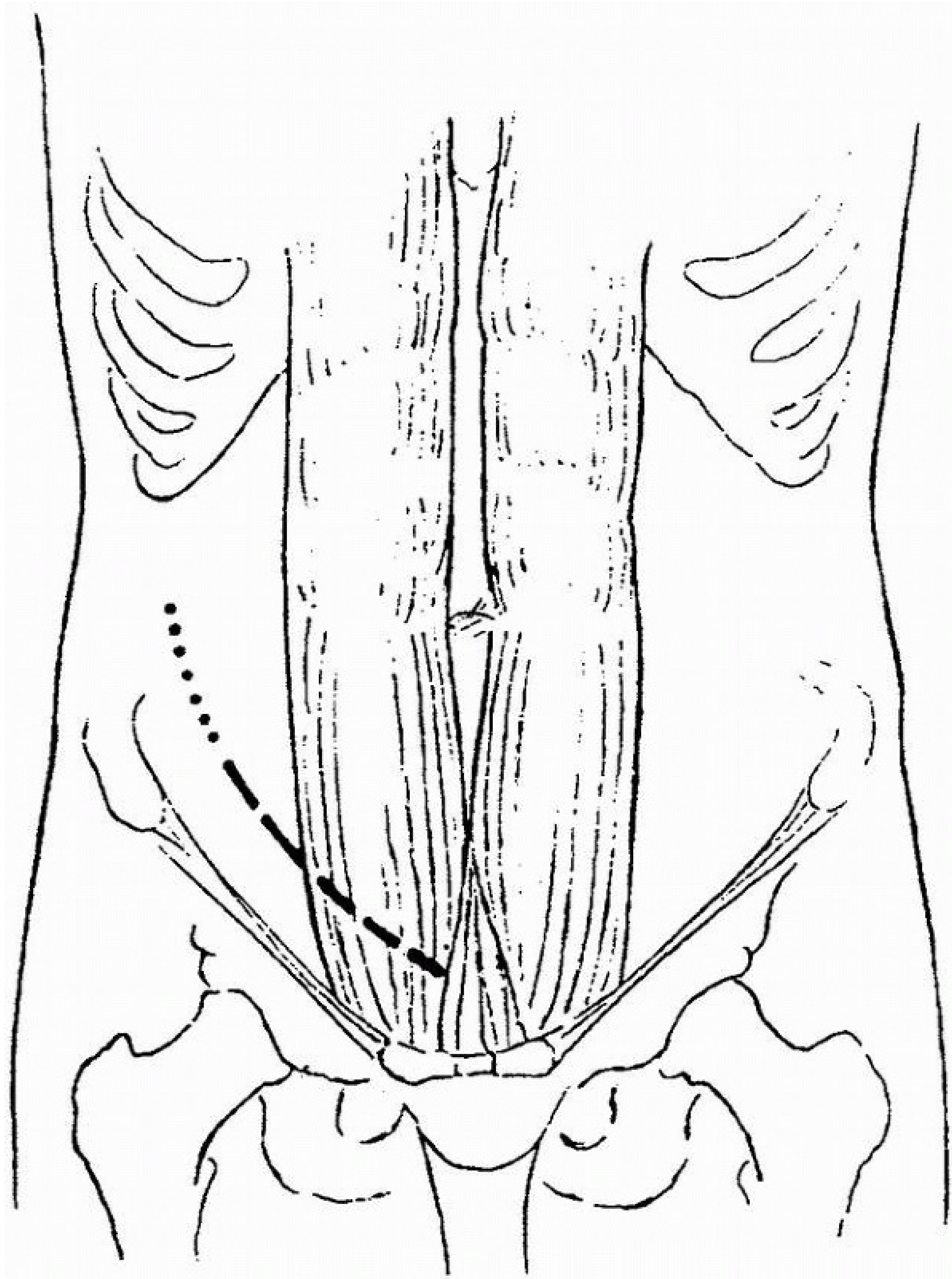


FIGURE 8.1 Standard incision for adult kidney transplantation. An oblique incision is made from the symphysis in the midline curving in a lateral and superior direction to the iliac crest.

Venous Anastomosis

Using a 5-0 polypropylene suture, the donor renal vein is usually anastomosed end to

side to the external iliac vein (Fig. 8.2). If there are multiple renal veins,

the largest may be used; the others can be ligated safely because of internal collateralization of the renal venous drainage. If two veins are about the same size, they can be sewn together with the "pair of pants" technique, or individually anastomosed to the external iliac vein. With deceased donor renal transplants, the donor vena cava may be used as an extension graft for the short, right renal vein. The venous anastomosis is usually done first to minimize ischemia to the leg.

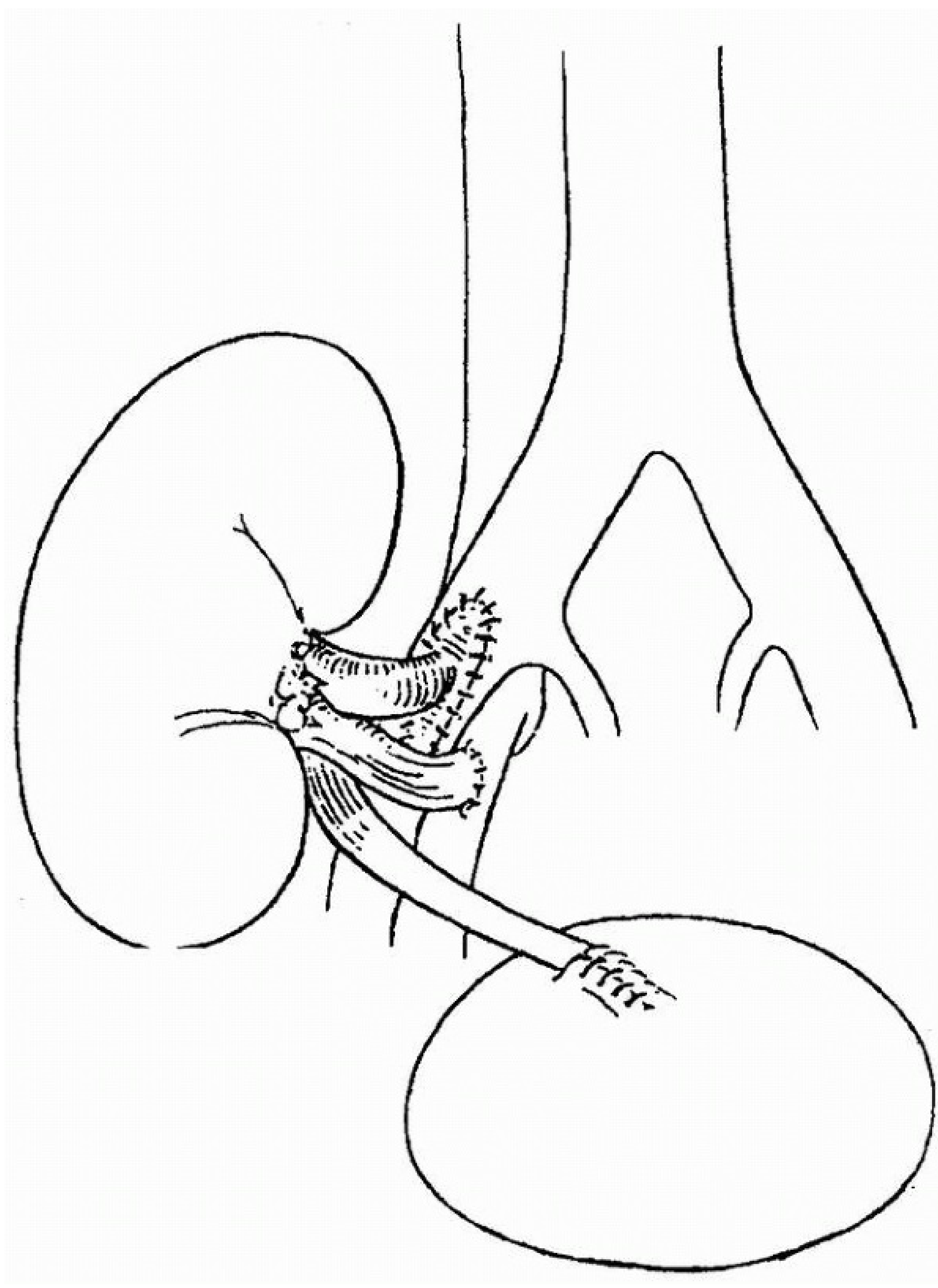


FIGURE 8.2 The standard hookup. The donor renal artery is shown anastomosed end to side on a Carrel aortic patch to the recipient external iliac artery. The donor renal vein is anastomosed to the recipient external iliac vein. The donor ureter is anastomosed to the recipient bladder with an antireflux technique.

Arterial Anastomosis

The donor renal artery is usually sewn to the external iliac artery in an end-toside fashion using a 5-0 or 6-0 polypropylene suture (Fig. 8.2). In a deceased donor kidney transplantation, the donor renal artery or arteries are usually kept in continuity with a patch of donor aorta called a *Carrel aortic patch,* which makes the end-to-side anastomosis much easier and safer, and facilitates the anastomosis of multiple renal arteries. In a living related donor transplantation, a Carrel patch is not available, and the renal artery is sewn to the recipient artery. In small children and in patients undergoing repeat transplantation on the same side, it may be necessary to use arteries other than the external iliac artery. The aorta, common iliac artery, or hypogastric artery is sometimes used. During the anastomosis time, the kidney is wrapped in a gauze pad with crushed ice saline to minimize warm ischemia.

Multiple Arteries

A variety of techniques have been proposed for handling donors with multiple renal arteries. In no case should a lower pole artery be sacrificed because this may lead to ureteral necrosis. There may be visible capsular vessels that supply a tiny part of the cortical surface of the kidney. These vessels may be ligated, and tiny superficial ischemic areas on the surface of the kidney may result. In deceased donor transplantations, it is best to keep all the arteries on a single large Carrel aortic patch and to sew the Carrel patch to the recipient vessel. If there are multiple arteries in a living donor transplant, or if a Carrel patch is not available, the donor arteries can be anastomosed individually or anastomosed to each other before being anastomosed to the recipient vessel. Occasionally, a small lower-pole branch may be anastomosed end to end to the inferior epigastric artery. For recipients with multiple donor arteries, it may be helpful to administer 1000 units of intravenous heparin by bolus before suturing the arterial anastomoses, with a continuation of the heparin infusion at 100 units per hour for the duration of the hospitalization.

Ureter Anastomosis

The ureter can be anastomosed to the recipient bladder or into the ipsilateral native

ureter as a ureterostomy. The native ureter may also be brought up to the allograft renal pelvis as a ureteropyelostomy. Most surgeons use the bladder whenever possible. Preferably, the recipient's bladder will have been shown to be functional before the transplantation; however, even small, contracted bladders that have not “seen” urine for prolonged periods usually regain function and capacity. If necessary, the ureter can be connected to a previously fashioned ileal or colonic conduit.

There are several ways of reimplanting the ureter into the bladder. The most common approach is one in which the ureter is reimplanted extravesically, using the *Lich-Gregoir* technique. First, the bladder is distended with saline, and the extravesical tissues are dissected from the detrusor muscle. A muscular tunnel is then created by separating the detrusor muscle from the bladder mucosa for a length of about 2 to 4 cm. The ureter is prepared by removing redundant ureteral length, preserving adequate distal blood supply, and spatulating posteriorly. A mucosal opening is created, and interrupted or running degradable suture, preferentially polydioxanone surgical suture, is used to approximate the ureteral and bladder mucosa. Finally, the detrusor muscle is closed exteriorly to create an antireflux mechanism (Fig. 8.3). Absorbable suture is used to prevent stone formation. Foley catheter drainage of the bladder is required for about 4 days, unless there are bladder abnormalities that may necessitate longer drainage.

Other, less common approaches include the *Barry* technique, the singlestitch *Taguchi* technique, and the intravesical *Leadbetter-Politano* technique. Whichever technique is used for the ureteral anastomosis, an indwelling stent should be placed in most cases. In a recent meta-analysis by Mangus and Haag, the urinary complication rate following routine stenting was 1.5% compared with 9% without stenting ($P < .0001$). Routine stenting has also proved

---

cost-effective because of the hospital costs associated with a single urinary complication. Additionally, stents are well tolerated by transplant recipients because the location of the ureter high in the bladder dome and kidney denervation result in minimal trigonal irritation and reflux pain. With the use of cotrimoxazole for prophylaxis against *Pneumocystis carinii*, and the removal of stents 3 to 4 weeks after transplantation, the incidence of urinary tract infections among stented recipients remains low. Clear notation of stent placement and its subsequent removal must be made to prevent inadvertent stent retention. Because a retained stent may be difficult to remove intact and may be a source of recurrent urinary tract infections and ureteral stones.

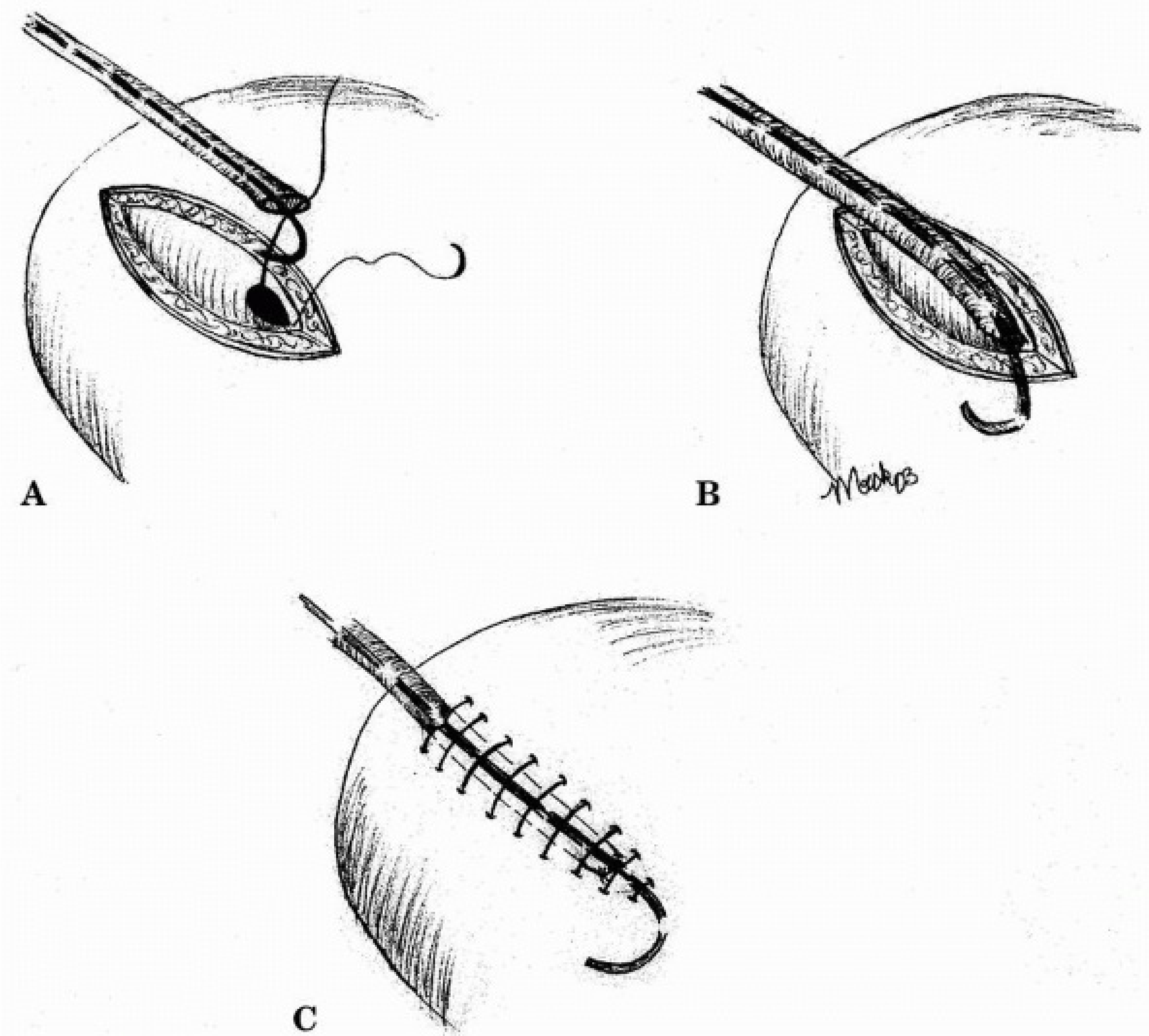


FIGURE 8.3 A Lich-Gregoir reimplantation. A single, small opening is made in the bladder (A), and the ureter is sewn to the bladder mucosa over a ureteric stent (B). The bladder muscle is used to create an antireflux mechanism (C).

Drains

Drains may be placed through a separate small incision into the perirenal space to drain blood, urine, or lymph. Some surgeons routinely place drains, whereas others do not. Closed drains, such as the Jackson-Pratt type, are preferred over the open Penrose-type drains because of a lower risk for wound infection. Placing a drain at the end of the procedure and leaving it for the initial postoperative course has been shown to reduce the incidence of lymphoceles. Drains should typically be removed once the output is less than 100 mL per day.

Intraoperative Fluid Management

Adequate perfusion of the newly transplanted kidney is critical for the establishment of an immediate postoperative diuresis and the avoidance of delayed

graft function (see Chapter 9). Volume contraction should be avoided and mild volume expansion maintained, conducive to the recipient's cardiac status. Central venous pressure should be maintained at about 12 mm Hg with the use of isotonic saline and albumin infusions, and mean arterial pressure should be kept above 80 mm Hg.

Before the release of the vascular clamps, a large dose of methylprednisolone is usually given. If an antibody induction agent is being used (see Chapter 5), it should be administered before this time. Mannitol and furosemide are also given, and fluid replacement is maintained accordingly. Postoperative management is discussed in Chapter 9.

En Bloc and Dual Kidney Transplantation

At the extremes of donor age, both donor kidneys are sometimes transplanted into a single recipient. The simultaneous use of both kidneys entails some additional technical risks to the recipient. Their use is a reflection of the donor shortage and reluctance to discard functional organs.

For donors younger than 2 years of age, both kidneys are usually transplanted *en bloc* with the donor aorta and vena cava (Fig. 8.4). For donors between the ages of 2 and 5 years, the surgeon decides whether there is sufficient nephron mass to separate the kidneys and provide allografts for two individuals. Separation can be considered when the allograft measures greater than 6 cm in length (the donor weight is usually > 15 kg). For the *en bloc* procedure, the aorta and vena cava superior to the renal vessels are typically closed with 6-0 nonabsorbable monofilament suture. All the other branches of the great vessels are carefully ligated with 4-0 silk ties, the infrarenal aorta is then anastomosed to the external iliac artery, and the infrarenal vena cava is anastomosed to the external iliac vein. The renal vessels should not be compromised when oversewing the suprarenal aorta and vena cava.

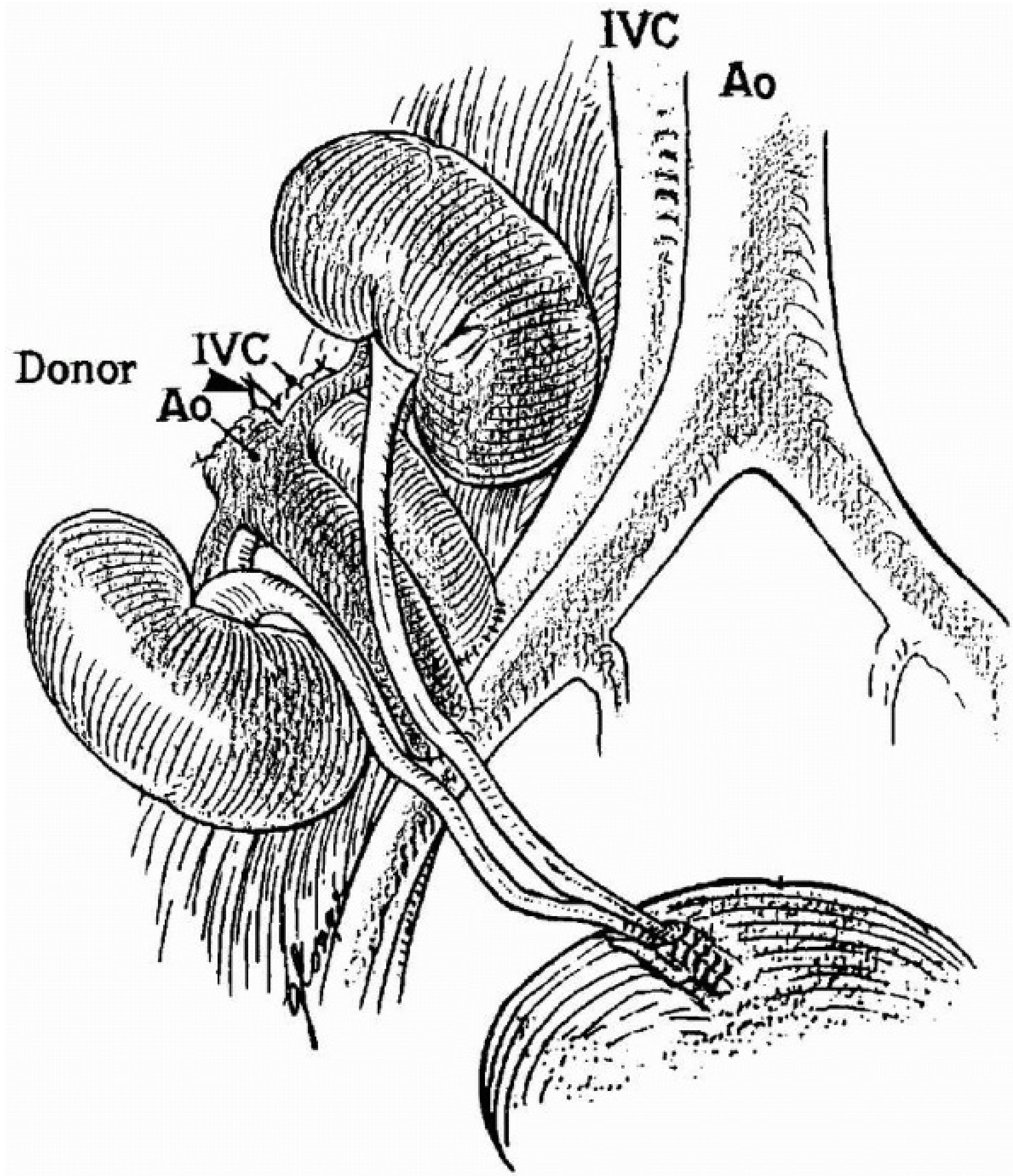


FIGURE 8.4 Pediatric *en bloc* kidney transplantation. The donor aorta (*Ao*) and inferior vena cava (*IVC*) are anastomosed to the external iliac vessels. The ureters are anastomosed to the bladder using pediatric stents. (From Bretan PN, Koyle M, Singh K, et al. Improved survival of en bloc renal allografts from pediatric donors. J Urol 1997;157:1592—1595, with permission.)

The kidneys from pediatric *en bloc* donors must be carefully positioned to avoid kinking of the blood vessels, and the ureters should be greater than 6 cm to reach the bladder without tension. If the ureters are implanted into the bladder separately, and a complication occurs in one kidney, then the risk for compromising the other kidney is reduced. The rate of technical complications, most typically urine leaks and vascular thrombosis, varies between 10% and 20% with young donor kidneys transplanted

individually or *en bloc*. The rate of thrombosis may be reduced by using a very low dose of an anticoagulant, such as intravenous heparin at 100 to 200 units per hour for the duration of the hospitalization, and converting to aspirin (81 mg) daily for 3 months.

Kidneys from older "marginal" donors are sometimes discarded for fear they will not provide adequate renal function for their recipients. To avoid this waste, some centers now advocate the use of both kidneys (dual transplantation) from donors aged 60 years or older. Dual transplantation is appropriate if the calculated creatinine clearance is less than 90 mL per minute at the time of admission, or if there is evidence of significant histologic damage on the biopsy specimen taken at the time of organ retrieval. These kidneys are typically placed into older recipients who are not significantly obese and whose metabolic requirements may be less. One kidney can be placed in each iliac fossa by using a preperitoneal midline incision or separate lower abdominal Gibson incisions. Alternatively, both kidneys can be placed on one side, preferably the right. For a unilateral incision, the right kidney is typically placed superolaterally, and the right renal vein with donor vena cava extension is anastomosed to the recipient vena cava. The right renal artery is then anastomosed to the common iliac artery. After revascularization of the right kidney, the left kidney is then placed in a more inferomedial position. The left renal vein and artery are anastomosed to the external iliac vessels (Fig. 8.5). The survival rate of dual kidneys is about 7% less than that for single kidneys, although when compared with the survival rate of single kidneys from donors older than 60 years, their outcome is similar.

SURGICAL COMPLICATIONS OF KIDNEY TRANSPLANTATION

The clinical presentation of surgical and nonsurgical complications of kidney transplantation may be similar. Graft dysfunction may reflect rejection or a urine leak; fever and graft tenderness may reflect wound infection or rejection. Post-transplantation events have a broad differential diagnosis that must include technical complications of surgery as well as immunologic and other causes.

The fundamental algorithm in the management of post-transplantation graft dysfunction requires that vascular and urologic causes of graft dysfunction be ruled out before concluding that an event is a result of a medical cause such as rejection or cyclosporine toxicity. The differential diagnosis of postoperative graft dysfunction is discussed in Chapter 9, and the radiologic diagnostic tools are discussed in Chapter 13. Doppler ultrasound is invaluable in the differentiation of medical and surgical postoperative complications.

Wound Infection

In the 1960s and 1970s, wound infection rates after kidney transplantation were as high as 25%. Wound infections now occur in less than 1% of cases. This

improvement is a result of several factors: patients receiving transplants are healthier;

lower steroid doses are used for both maintenance and treatment of rejection; and perioperative antibiotics are routinely used. Obviously, strict aseptic technique in the operating room is essential to prevent wound infection. If infections do occur, they should be treated with drainage and systemic antibiotics to avoid contamination of the vascular suture line and possible mycotic aneurysm formation. Patients who are obese or receiving the immunosuppressant agent sirolimus have a significantly higher incidence of wound infections.

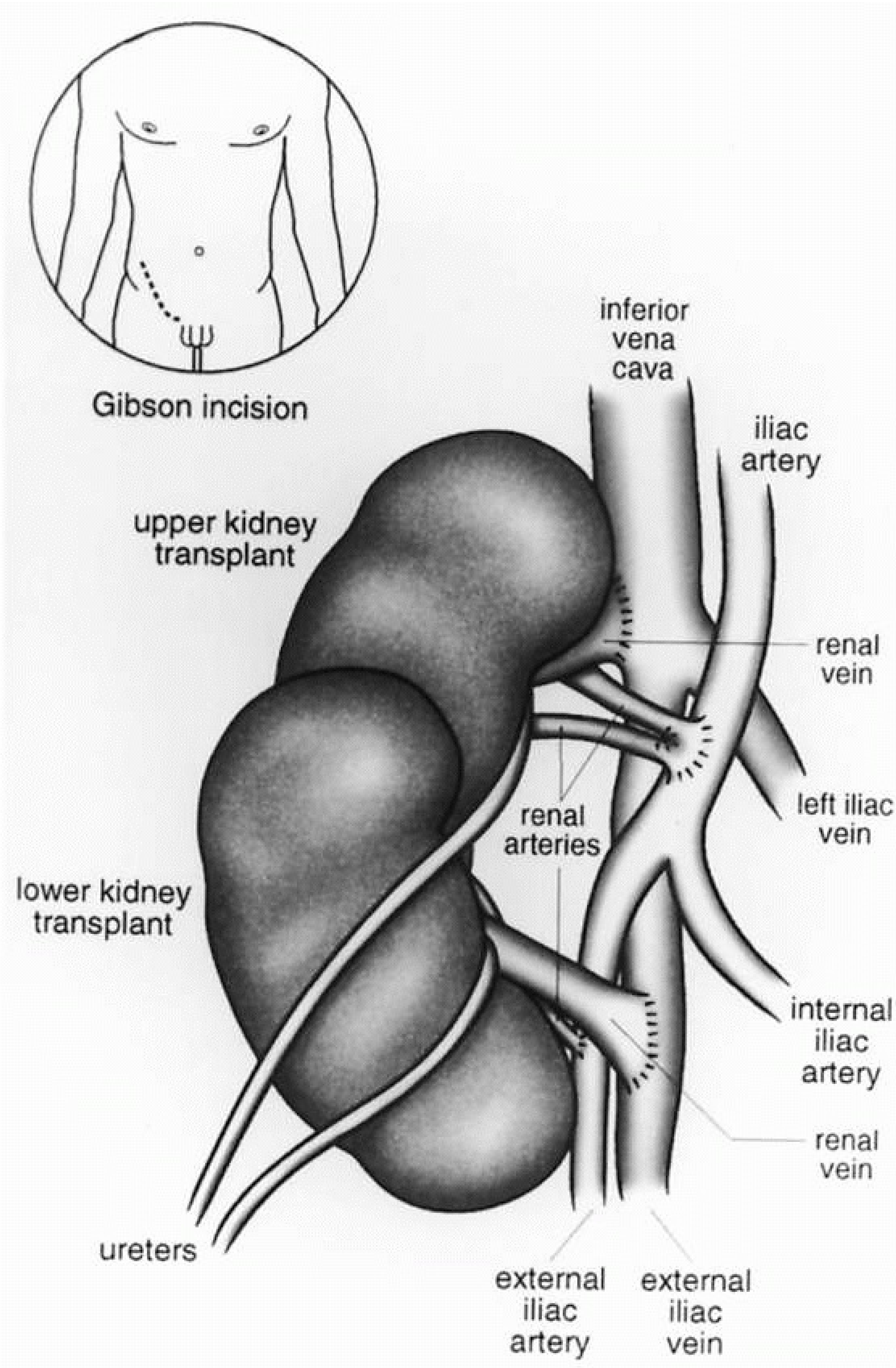


FIGURE 8.5 Dual transplantation of adult kidneys into a single recipient. (From Masson D, Hefty T. A technique for the transplantation of 2 adult cadaver kidney grafts into 1 recipient. J Urol 1998;160:1779—1780, with permission.)

Lymphocele

Lymphoceles are collections of lymph caused by leakage from severed lymphatics surrounding the iliac vessels or the renal hilum of the donor kidney. The incidence of lymphoceles reported in the literature varies widely. Some lymphoceles are small and asymptomatic. Usually, the larger the lymphocele, the more likely it is to cause pain, ureteral obstruction, or venous compression. Lymphoceles occasionally produce incontinence secondary to bladder compression, scrotal masses secondary to spontaneous drainage into the scrotum, or vena cava obstruction that can result in deep vein thrombosis (DVT) or leg swelling. The incidence of lymphoceles can be reduced by minimizing the pelvic dissection, ligating lymphatics, and avoiding sirolimus in the early postoperative period. Additionally, placing an intraoperative drain and leaving it for the initial postoperative course has been shown to reduce lymphatic collections.

Lymphoceles are usually diagnosed by ultrasound (see Chapter 13). The characteristic ultrasound finding is a roundish, sonolucent, septated mass medial to the renal allograft. Hydronephrosis may be present, and the ureter may be seen adjacent to and compressed by the lymphocele. More complex internal echoes may signal an infected lymphocele. Usually, the clinical situation and ultrasound appearance distinguish a lymphocele from other types of perirenal fluid collections, such as hematoma or urine leak. Simple needle aspiration of the fluid using sterile technique makes the diagnosis. The fluid obtained is clear and has a high protein content, and the creatinine concentration is equal to that of serum.

No therapy is necessary for the common, small, asymptomatic lymphocele. Percutaneous aspiration should be performed if there is suspicion of a ureteral leak, obstruction, or infection. The most common indication for treatment is ureteral obstruction. If the cause of the obstruction is simple compression caused by the mass effect of the lymphocele, drainage alone will resolve the problem. The ureter itself is often narrowed and may need to be reimplanted because of its involvement in the inflammatory reaction in the wall of the lymphocele. Repeated percutaneous aspirations are not advised because they seldom lead to dissolution of the lymphocele and often result in infection.

Infected or obstructing lymphoceles can be drained externally using either a closed or an open system. Closed systems are superior because they control the fluid and are less susceptible to infection. Sclerosing agents, such as povidone iodine (Betadine), tetracycline, or fibrin glue, can be instilled into the cavity with good results. Lymphoceles can also be drained internally by marsupialization into the peritoneal cavity, where the fluid is resorbed. Marsupialization can be done as an open surgical procedure or laparoscopically. It is important to ensure that the opening in the lymphocele is large enough to prevent peritoneal closure, which can produce

recurrence or bowel entrapment and incarceration. Omentum is often interposed in the opening to prevent closure. Care must be taken to avoid injury to the ureter, which may lie in the wall of the lymphocele. On rare occasions, the actual site of lymph leak can be identified and ligated.

Bleeding

The risk for postoperative bleeding can be minimized by close attention to pretransplantation coagulation parameters, which should be considered during the pretransplantation workup (see Chapter 7). Aspirin and anticoagulant medications should be discontinued when possible before transplantation. Meticulous preparation of the allograft and hemostasis during the operation minimizes this risk for bleeding. If there is significant blood loss at the time of reperfusion, the vascular clamps should be reapplied and the graft carefully inspected. Anastomotic bleeding can usually be controlled with fine suture ligatures, and oozing will usually stop with gentle pressure and cellulose gauze. Early postoperative bleeding can occur from small vessels in the renal hilum, which may not have been apparent before closure because of vasospasm. After surgery, when perfusion improves, these hilar vessels can then bleed. Close observation of vital signs and serial hematocrits is necessary for the first several postoperative hours to recognize this type of bleeding. If postoperative bleeding occurs, coagulation parameters should be studied to ensure that there is no occult coagulopathy. Administration of blood, efficient dialysis, estrogen infusions, and vasopressin

---

may help in avoiding surgical exploration. Ultrasound can help to confirm and monitor a perigraft hematoma. If more than 4 units of blood are required within 48 hours, operative evacuation of the hematoma will usually accelerate graft function and patient comfort. Late profound hemorrhage can result from the rupture of a mycotic aneurysm. Nephrectomy and repair of the artery are usually required. Rarely, the external iliac artery may have to be ligated and blood supply to the ipsilateral leg provided by extra-anatomic bypass.

Thrombosis

Renal Artery Thrombosis

Renal artery thrombosis is most often seen in patients with thrombotic tendencies (see Chapter 7). It can also occur in kidneys with multiple arteries or when significant atherosclerosis is present in the donor or recipient vessels. Renal artery thrombosis occurs most often within the first 2 to 3 days after transplantation. The patient may experience a sudden cessation of urine flow without any discomfort. Thrombocytopenia and hyperkalemia may occur as platelets are consumed in the graft with a sudden elevation in creatinine. The diagnosis is made by Doppler ultrasonography or renal scan

because no blood flow is seen to the allograft. Unfortunately, most grafts that develop arterial thrombosis are lost. Rarely, the diagnosis is made immediately, and the allograft is salvaged by rushing the patient to the operating room for emergent arteriotomy and thrombectomy. Recipients with significant risk factors for arterial thrombosis should be anticoagulated.

Renal Vein Thrombosis

Renal vein thrombosis typically occurs in the early postoperative period and may result from kinking of the renal vein, stenosis of the venous anastomoses, hypotension, hypercoagulable state, and acute rejection. With intraoperative venous thrombosis, the allograft appears swollen and cyanotic, and a clot may be palpable in the renal vein. Delayed renal vein thrombosis is usually diagnosed by Doppler ultrasonography because a clot may be visualized in the vein with decreased blood flow to the allograft. Although thrombolytic therapy may be helpful, when possible, emergent thrombectomy with revision of the anastomosis should be attempted. Unfortunately, these grafts are usually lost because of the prolonged ischemia time and require allograft nephrectomy.

Deep Vein Thrombosis

DVT can extend into the renal vein or cause life-threatening pulmonary embolism. Kidney transplant recipients are at a moderate risk for developing DVTs. Possible reasons for this include stasis of the iliac vein from clamping during creation of the vascular anastomoses, endothelial injury, pelvic dissection, immobility, and perioperative dehydration. Ultrasonic imaging is highly sensitive and specific in detecting proximal DVTs but far less satisfactory in detecting distal thrombi because of poor visualization of the calf veins. Patients with DVTs should receive anticoagulation therapy for at least 3 months. Heparin therapy is overlapped with initiation of warfarin, heparin can be discontinued after 5 days provided the INR has been therapeutic for 2 consecutive days (INR 2.0 to 3.0). Heparin is cleared by the kidney; therefore, transplant patients with renal insufficiency can become dangerously over-anticoagulated. The platelet count should be monitored for heparin-induced thrombocytopenia. Inferior vena cava filters should be inserted in patients with contraindications to anticoagulation. Prevention of venous thrombosis in transplant recipients should include intermittent pneumatic compression stockings that are fitted appropriately as well as early ambulation. The addition of 5000 U of unfractionated heparin subcutaneously is appropriate in high-risk recipients; however, there is a substantial risk for hemorrhagic complications in patients with renal insufficiency, and therefore no more than twice-daily dosing is advisable perioperatively. Outpatient therapy with low-molecular-weight heparin is unsuitable for renal transplant recipients because the degree of anticoagulation may be unpredictable and difficult to monitor. Aspirin is a better alternative and appears to provide adequate outpatient protection from thrombosis.

Renal Artery Stenosis

Transplant renal artery stenosis (TRAS) has been reported to occur in up to 10% of recipients. Imaging with angiography remains the gold standard; however, it is often suspected on ultrasonography because administration of contrast is not recommended in patients with marginal renal function. A peak systolic velocity greater than 250 cm per second and a "tardus-parvus" arterial waveform are both suspicious for TRAS. If stenosis is suspected in the first postoperative month, then surgical revision of the anastomoses is usually the best option. Graft loss after surgical repair has been reported in up to 30% of cases and is a reflection of the difficulty in directly approaching the vascular anastomosis in a noncollateralized kidney. Beyond 1 month, percutaneous transluminal angioplasty is usually favored. Table 8.1 lists potential causes of stenosis. The term *pseudorenal artery stenosis* has been used to describe the situation that can occur if an atherosclerotic plaque in the iliac vessels impairs blood flow to the transplant renal artery. To avoid suture line stenosis, the running suture should not be overly tightened, especially if it is an end-to-end arterial anastomosis. The postulate that rejection can cause renal artery stenosis has not been conclusively proved.

Urine Leaks

Urinary extravasation may be a result of distal ureteric ischemia because the allograft ureter receives blood supply solely from the renal artery. Therefore, the preservation of a lower pole donor renal artery is essential to ensure the viability of the ureter. Performing a careful donor nephrectomy and leaving the shortest length of ureter that allows for a tension-free bladder anastomosis helps to ensure that the distal ureter has adequate blood supply. A stented

Lich-Gregoir ureteric anastomosis to the bladder has a low incidence of urinary leaks. A leak may also occur at the level of the renal pelvis or calyx and may result from obstruction. Leaks typically occur within the first few days after transplantation or at the onset of post-transplantation diuresis in patients with delayed graft function. The general presentation is increasing wound drainage, decreasing urine output and allograft tenderness. A leak may also cause the recipient to experience abdominal or scrotal pain and swelling. The diagnosis is made by a significantly elevated creatinine of the fluid drained from the incision when compared with the plasma. The diagnosis is typically confirmed by cystogram, nuclear medicine scan or antegrade nephrostogram.

TABLE 8.1 Potential Causes of Renal Artery Stenosis

Rejection of the donor artery

Atherosclerosis of the recipient vessel

Clamp injury to the recipient or donor vascular endothelium

Perfusion pump cannulation injury of the donor vessel

Faulty suture technique: pursestring effect, lumen encroachment by the suture, improper suture material, fibrotic inflammatory reaction to polypropylene in the setting of abnormal hemodynamics

End-to-end anastomosis with abnormal fluid dynamics

Angulation as a consequence of disproportionate length between graft artery and iliac artery

End-to-end anastomosis with vessel size disproportion

Pseudorenal artery stenosis by critical iliac atherosclerotic lesion

Kinking of the renal artery

A Foley catheter should be immediately placed if there is clinical suspicion of a leak. The catheter reduces intravesical pressure and occasionally may reduce or stop leakage altogether. Percutaneous antegrade nephrostomy may be used to diagnose the leak and control the flow of urine. Some leaks can be managed definitively with external drainage and stent placement alone. If the leak is caused by a ureteral slough, percutaneous treatment will never work and only delays definitive treatment. For these reasons, when leaks occur, early surgical exploration and repair are usually required.

The type of surgical repair depends on the level of leak and the viability of the tissues. If a ureteral leak is a simple anastomotic leak, resection of the distal ureter and reimplantation is the easiest solution. If the ureter is nonviable because of inadequate blood supply, ureteropyelostomy using the ipsilateral native ureter is a good option. Cystopyelostomy has also been done to replace a necrotic ureter. The bladder is mobilized and brought directly to the allograft renal pelvis without an intervening ureter. The bladder may need to be fixed superiorly by a *Psoas hitch* or extended by a *Boari flap*.

Ureteral Obstruction

Common causes of obstruction include catheter blockage, blood clots, extrinsic ureteric compression, ureteral stricture, stones, and prostatic hyperplasia. Lowgrade obstruction in the early postoperative period may be a result of edema with vigorous diuresis and usually resolves. Obstruction is usually manifested by impairment of graft function and increasing hydronephrosis, it may be painless because of the absence of innervation to the transplanted kidney. Placement of an antegrade nephrostomy tube can rapidly reduce obstruction while serving as a conduit for an antegrade nephrostogram to help confirm the diagnosis.

The Foley catheter should be checked for blockage. Minor ureteric obstruction may resolve with proximal diversion and stenting. Ureteric strictures smaller than 2 cm can be treated endoscopically with a laser or cutting blade, balloon dilation, and stenting (Fig. 8.6). Ureteric strictures larger than 2 cm require open surgery with excision and reimplantation. If the length of the ureter is compromised, ureteropyelostomy using the ipsilateral native ureter or cystopyelostomy is a reasonable alternative. Extrinsic ureteric compression can often be successfully treated with external drainage of the lymphocele, hematoma, or urinoma.

Gastrointestinal Complications

The incidence of colonic pseudo-obstruction (Ogilvie syndrome) is increased in renal transplant recipients, although the overall mortality rate for perforated colon in this immunosuppressed population is as high as 60%. Post-operatively, renal transplant recipients tend to develop constipation owing to inactivity, dehydration, electrolyte abnormalities, diabetes, and narcotic analgesia. As the colon expands, the tissue

strength is reduced. Immunosuppression with corticosteroids exacerbates this process, increasing the vulnerability to perforation by

causing atrophy of the intestinal lymphatics and further thinning the bowel wall. When Ogilvie syndrome is recognized (pancolonic dilation ≥10 cm in the absence of an obstructive lesion), patients should receive “nothing per oral,” have opiates withdrawn and steroid doses tapered. If the renal allograft is functioning well, the addition of neostigmine usually proves efficacious; however, the drug is contraindicated in patients with renal insufficiency. Colonic decompression with a rectal tube or expertly performed colonoscopy is indicated for patients who have failed to respond to conservative therapy after 24 to 48 hours. To prevent catastrophic consequences of perforation, emergent laparotomy is indicated in patients who show signs of peritonitis or clinical deterioration. Although transplantations are typically performed through an extraperitoneal approach, obese patients on high doses of steroids should probably receive “nothing per oral” until flatus in the immediate postoperative period.

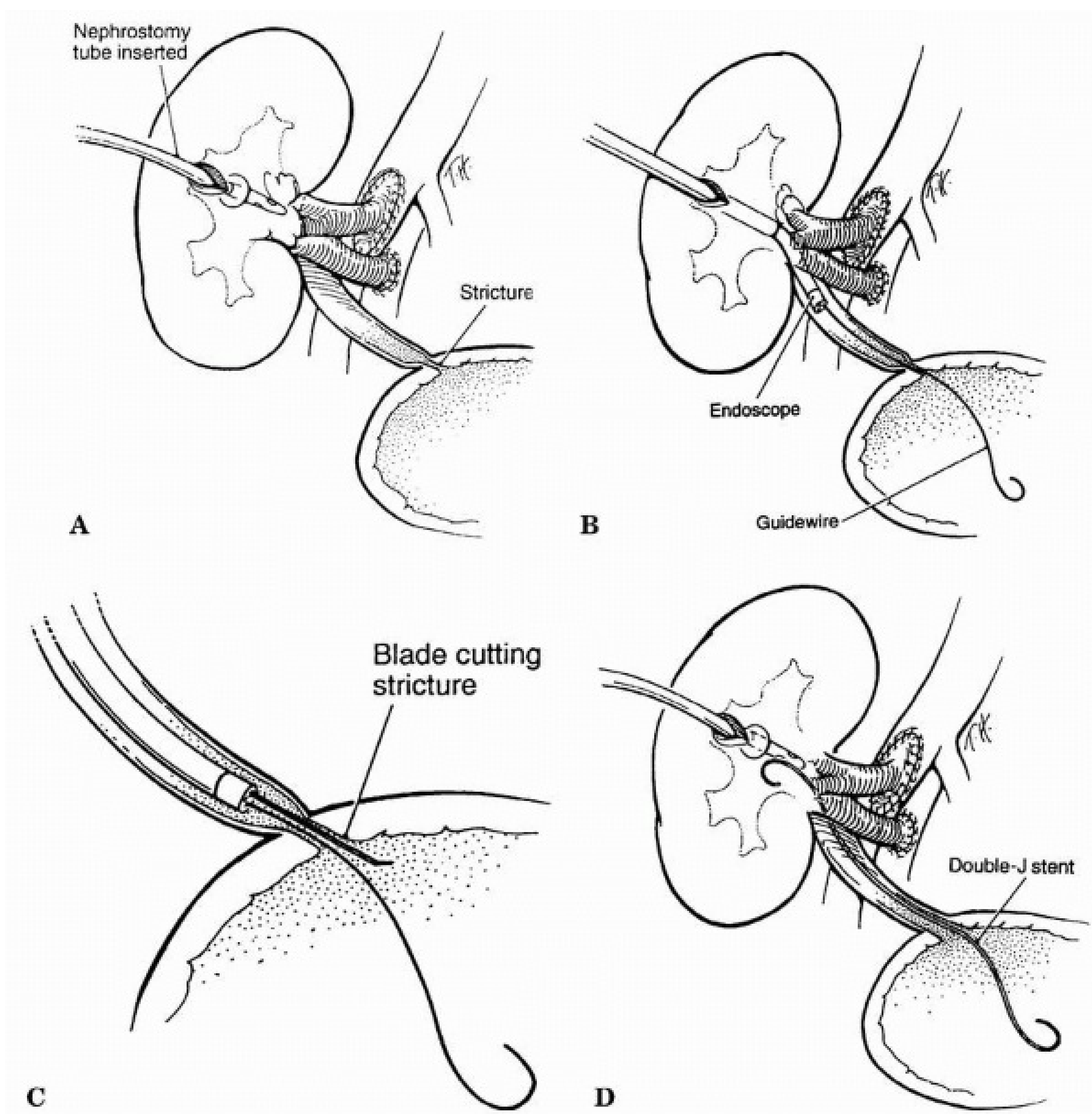


FIGURE 8.6 Stages in the endourologic treatment of ureteral structure.

Other gastrointestinal complications are fairly common and may be related to bowel injury that occurred during the procedure, or medications such as mycophenolate mofetil. Sodium polystyrene sulfonate (Kayexalate)sorbitol enemas should not be administered to uremic patients because they have been associated with colonic necrosis. Sodium phosphate (Fleet) enemas should be avoided in patients with poor renal function because of the high phosphate load.

ALLOGRAFT NEPHRECTOMY

Indications

Kidneys that have failed either for technical reasons or because of rejection may need to be removed. Indications for allograft nephrectomy are symptoms and signs that typically occur when immunosuppression is withdrawn but may be delayed by weeks or months. These can include low-grade fever, graft tenderness, and hematuria. It may be possible to lessen the symptoms and avoid nephrectomy by temporary reinstitution of steroids. Avoidance of nephrectomy is preferred because the procedure can result in significant morbidity and may cause a steep elevation in the percentage of preformed cytotoxic antibodies affecting future transplantations. If the graft loss is acute and occurs within 1 year of transplantation, nephrectomy is necessary in most cases. Graft loss from chronic rejection after 1 year may not require nephrectomy. The rejected graft that remains *in situ* typically becomes a small, fibrotic mass. Acquired cystic disease may develop as described in chronically diseased native kidneys.

Procedure

The removal of a failed allograft may be technically more difficult than the transplantation itself because of the inflammatory response and scarring as a consequence of rejection. For this reason, the procedure should be performed at centers with appropriate experience. Usually, the old incision is reopened. Care must be taken to avoid the peritoneum, which may be draped across the surface of the kidney. If the nephrectomy is performed soon after transplantation, the kidney can be removed entirely because it is not very adherent to surrounding structures. If there has been recurrent rejection, the kidney usually adheres to surrounding structures and needs to be removed subcapsularly. It is almost always safe to leave a small amount of donor vessel in the recipient; this additional vessel length can help the surgeon achieve hemostasis with suture ligation.

Hemostasis should be meticulous. Some dead space is always left after nephrectomy. If this fills with blood, abscess formation is more likely. Although a closed drain may be

used, it may inadequately drain the blood and create the potential for infection by its presence. Electrocoagulation of the entire raw surface of the capsule should be performed, and spraying thrombin topically may improve hemostasis. Topical and parenteral antibiotics are routinely used.

Complications

Although there are few series in the literature, the reported morbidity for allograft nephrectomy is high. The potential complications include acute bleeding during surgery secondary to injury to the iliac artery or vein; injury to other surrounding structures, such as the bowel; infection; and lymph leaks. Leaving small segments of the allograft renal artery or vein does not usually cause longterm problems, although rupture can occur if the vessels become secondarily infected. Likewise, leaving a small amount of allograft ureter in place can result in some gross hematuria after the allograft nephrectomy; the hematuria is almost always limited and usually does not require reoperation.

NON—TRANSPLANT-RELATED SURGERY

Immunosuppressed transplant recipients may occasionally require significant surgical intervention not directly related to the transplantation, such as coronary artery bypass, cholecystectomy, hip replacement, or gynecologic procedures. Nephrologists or members of the transplantation team are often requested to aid in the perioperative management of such patients, and certain precautions are required (Table 8.2).

TABLE 8.2 Precautions for Kidney Transplant Recipients Undergoing Post-transplantation Surgical Procedures

Maintain hydration.
Use non-nephrotoxic prophylactic antibiotics.
Give calcineurin inhibitor by mouth when possible and modify intravenous dose when necessary.

Ensure adequate imaging studies have been obtained to avoid injury to the allograft and ureter.

Provide perioperative steroid coverage.

Adjunctive immunosuppressants can be held for several days.

Avoid nephrotoxic antibiotics and analgesics.

Monitor graft function and plasma potassium and acid-base status.

Consider wound healing impairment.

The renal function of many transplant recipients is impaired to varying degrees, and the capacity to concentrate urine and lower urinary sodium concentration may be limited. Maintenance of hydration is, therefore, particularly important perioperatively to avoid further reduction in renal function. If a patient will be unable to take immunosuppressive medications orally for more than 24 hours, calcineurin inhibitors should be given intravenously in a dose that is about one third of the total daily oral dose (see Chapter 5) over 4 to 8 hours. Although functional adrenal suppression in patients taking 10 mg per day or less of prednisone is uncommon, a “stress dose” of 100 mg of hydrocortisone is typically given every 8 hours postoperatively until the patient can return to the preoperative oral prednisone dose. Additional agents, such as mycophenolate mofetil or rapamycin, can be safely withheld for 2 to 3 days. Nonnephrotoxic antibiotics should be given prophylactically, and if intravenous contrast is required for radiologic studies, a saline diuresis should be maintained. In patients with markedly impaired graft function, careful monitoring of postoperative plasma potassium levels and acid-base status is mandatory.

SURGICAL CONSIDERATIONS IN CHILDREN

Urologic disease is the cause of renal failure in up to one third of children with end-stage renal disease (see Chapter 16). It is therefore important to study bladder function in children with a history of urinary tract infections or voiding abnormalities. Reconstructive surgery must be coordinated with possible renal transplantation. The parents and child must be psychologically prepared to perform intermittent catheterization, which may be necessary postoperatively.

The transplantation procedure for children who weigh more than 20 to 25 kg is generally the same as the procedure for adults. There may be an increase in complexity of the surgical procedure in the setting of prior bladder procedures, including augmentation or prior Mitrofanoff creation. The placement of the allograft and method of ureteral reimplantation must be carefully planned to avoid postoperative complications. In children smaller than 20 kg, comparatively large adult-size kidneys are implanted because kidneys from equivalently sized infant donors are more prone to technical complications. In the smallest recipients, we often place the venous anastomosis on the vena cava and the arterial anastomosis on the aorta in order to achieve the best position for the allograft in the right flank. In children who weigh more than 10 to 12 kg, an extraperitoneal approach can still be used. The right side is almost always preferable because of the easier exposure of the common iliac vessels. In children who weigh less than 10 to 12 kg, a midline transabdominal approach is generally necessary. The great vessels are approached by mobilizing the cecum, and the kidney is placed behind the cecum. To provide room for a large kidney in the right flank, a right native nephrectomy is sometimes necessary at the time of transplantation to create room for the allograft. Concomitant unilateral versus bilateral native nephrectomy should also be considered in recipients with a history of significant hydronephrosis, urinary obstruction, or urinary tract infection. In patients with severe hypertension refractory to multiple antihypertensive agents, bilateral native nephrectomy is generally performed before transplantation to avoid hypertension-related complications to the allograft. Before ureteroneocystostomy, we often place the transplanted ureter under the peritoneum, over the dome of the bladder, to avoid the potential for technical complications to the ureter should the child require exploratory laparotomy in the future.

Careful intraoperative fluid management is crucial to prevent thrombosis of large kidneys in small children. In general, generous fluid resuscitation with saline, colloid, and blood transfusions are necessary to provide adequate hemodynamic support before reperfusion. We consider a constant dialogue with the anesthesia service of paramount importance in this regard. In the smallest transplant recipients, reperfusion of a large kidney may consume a large portion of the circulating blood volume at reperfusion. In these patients, we generally administer blood transfusions in volumes of 10 mL/kg until the central venous and mean arterial pressures are adequate for reperfusion. We have

found this measure to be critical in avoiding early acute tubular necrosis that can be associated with hypotension and inadequate hemodynamic support before reperfusion. We also administer furosemide (1 mg/kg) and mannitol (0.125 to 0.25 g/kg) at the time of reperfusion to generate a diuresis. In general, intraoperative infusions with heparin are also administered to reduce the risk for graft thrombosis. We generally continue the heparin infusion postoperatively with a conversion to aspirin or warfarin, depending on a child's risk profile for graft thrombosis, as determined preoperatively (see Chapter 16).

Selected Readings

Aslam S, Salifu M, Ghali H, et al. Common iliac artery stenosis presenting as renal artery dysfunction in two diabetic patients. Transplantation 2001;71:814—817.

Bates SM, Ginsberg JS. Clinical practice: treatment of deep-vein thrombosis. N Engl J Med 2004;351:268.

Bruno S, Remuzzi G, Ruggenenti P. Transplant renal artery stenosis. J Am Soc Nephrol 2004;15:134—141.

Bunnapradist S, Gritsch HA, Peng A, et al. Dual kidneys from marginal adult donors as a source for cadaveric renal transplantation in the United States. J Am Soc Nephrol 2003;14:1031—1036.

Churchill BM, Steckler RE, McKenna PH, et al. Renal transplantation and the abnormal urinary tract. Transplant Rev 1993;7:21—25.

Langer R, Kahan BD. Incidence, therapy, and consequences of lymphocele after sirolimuscyclosporine-prednisone immunosuppression in renal transplant recipients. Transplantation 2002;74:804—808.

Mangus RS, Haag BW. Stented versus nonstented extravesical ureteroneocystostomy in renal transplantation: a meta-analysis. Am J Transplant 2004;4:1889.

O'Malley KJ, Flechner SM, Kapoor A, et al. Acute colonic pseudo-obstruction (Ogilvie's syndrome) after renal transplantation. Am J Surg 1999;6:492.

Pelletier SJ, Guidinger MK, Merion RM, et al. Recovery and utilization of deceased donor kidneys from small pediatric donors. Am J Transplant 2006;6:1646.

Rouviere O, Berger P, Beziat C, et al. Acute thrombosis of renal transplant artery. Transplantation 2002;73:403—409.

Saunders MD, Kimmey MB. Systematic review: acute colonic pseudo-obstruction. Aliment Pharmacol Ther 2005;22:917.

Veale JL, Yew J, Gjertson DW, et al. Long-term comparative outcomes between 2 common ureteroneocystostomy techniques for renal transplantation. J Urol 2007;177:632.

White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thromb Haemost 2003;90:446.

Editors: **Danovitch, Gabriel M.**
Title: ***Handbook of Kidney Transplantation, 5th Edition***

9

The "First Quarter:" The First Three Months After Transplantation

Alan Wilkinson

Kidney transplantation has reached a comforting state of success and maturity with well-defined stages that require special attention to particular aspects of patient care. These are usually defined as the early post-transplantation period, the first 3 months, and the later post-transplantation period, which encompasses all that happens for the remainder of the life of the transplant. The period discussed in this chapter ends at the beginning of the fourth month, although statistical analyses usually define the end of the first year as the onset of the late post-transplantation period. This division makes sense because many of the more acute events occur within the first 3 months, whereas from the end of the first year, patients are more stable. Rejection is most common in the early period, as are some of the more significant infections. Relatively high levels of immunosuppressants are used at this time, and the side effects are more marked than they are later on. The late period is discussed in the next chapter.

For most patients, this is one of the most exciting and yet anxious times in their life, and it is important to recognize this as we perform what for medical and transplant professionals have become quite routine tasks. The care of transplant recipients should ideally be a combined effort by medical and surgical teams that brings both their experience and expertise to the care of the patient. The best circumstance is for a single cooperative team to follow each patient together, making joint rounds and decisions about patient care. A relatively well-defined postoperative care pathway facilitates care, efficiency, and cost savings during this time of complex decision making. It is most useful to document all the events during the first admission in a manner that can easily be transmitted to the outpatient clinic. Some patients require readmission in this early period, and verbal and written communication between those caring for the patient in the clinic and the hospital is crucial to good care. The first 3 months are a time of relatively rapid change in management and also a time when surgical and immunologic complications are most common. It is sometimes tempting to focus most particularly on concerns related to graft function, immunosuppression, and rejection, but many of the medical issues discussed more completely in Chapter 10 are already present at this stage, and these too should be managed aggressively.

THE DAY OF THE OPERATION

Postoperative Assessment

Responsibility for the immediate postoperative care in the recovery room should be specifically designated to a member of either the surgical or medical team. This person must be familiar with the patient's preoperative medical history and evaluation as well as details of the source of the donor kidney. Because urine output is an important measure of early graft recovery, it is

necessary to know whether the patient had any preoperative urine output. The assessment should include ensuring hemodynamic and respiratory stability and assessment of volume status. The operative record and early laboratory results should be reviewed, paying particular attention to confirming that immunosuppression was given as ordered. The surgeon should discuss any unusual aspects of the operation with those taking over the patient's care. Most transplantation programs have a set of standard postoperative orders, and these should be completed. A sample set of orders is shown in Table 9.1. Institutions vary as to whether they transfer patients from the recovery room to an intensive care unit, a “step-down” unit, or a general ward. Most patients may be safely transferred directly to a general ward, but no matter where the patient goes, it is important that the staff there is experienced in the postoperative care of transplant recipients and familiar with the importance of measuring urine output, establishing volume replacement, and maintaining homodynamic stability. Strict control of blood glucose concentrations in all patients, not only diabetic patients, is important to facilitate recovery of the allograft and to promote healing.

TABLE 9.1 Suggested Postoperative Orders on Transfer of Kidney Transplant Recipient from the Recovery Room

Postoperative Nursing Orders*	
1.	Vital signs checked every hour for 12 hours, then every 2 hours for 8 hours, then every 4 hours for stable patients
2.	Intake and output every hour for 24 hours, then every 4 hours

3. Intravenous fluids per physician

4. Daily weight

5. Turn, cough, deep breathe every hour; encourage incentive spirometry every hour while awake

6. Out of bed first postoperative; ambulate daily thereafter

7. Head of bed at 30 degrees

8. Dressing changes daily as needed

9. Check dialysis access for function every 4 hours

10. No blood pressure; venipuncture in extremity with fistula or shunt

11. Foley catheter to bedside drainage, irrigate gently with 30 mL normal saline as needed for clots

12. Catheter care every 8 hours

13. Notify physician if urine output drops to less than 60 mL/h for 2 consecutive hours or greater than 300 mL/h for 4 hours or greater than 500 mL/h for 2 consecutive hours

14. Notify physician if systolic blood pressure, >180 mm Hg or <110 mm Hg

15. NPO until changed by surgical team

16. Chest radiograph immediately postoperatively

Postoperative Laboratory Orders

1. Complete blood count with platelets, electrolyte, creatinine, glucose, and blood urea nitrogen every 6 hours for 24 hours, then every morning

2. Calcineurin inhibitor level each morning

3. Chemistry panel including liver function tests; urine culture and sensitivity, twice weekly

With acknowledgement to Angela Phelps, RN and Elizabeth Hands, RN.

Fluid Replacement

There are probably almost as many protocols for intravenous fluid replacement as there are transplantation programs. The most important aspect is to ensure sufficient fluid replacement to maintain homodynamic stability and urine output, while avoiding making it necessary to dialyze patients who have received more fluid than the new allograft can adequately excrete. Patients are usually admitted for surgery somewhat above their “dry weight” and should be slightly hypervolemic at the end of surgery. If they are dialyzed preoperatively, it is best not to bring them to their dry weight, but to leave them about 1 kg over this. If all the urine passed is replaced, this overhydrated state will persist, and the protocol should allow for this by progressively reducing the volume replaced, provided urine output and blood pressure are adequate. It is useful to separate fluid replacement into “maintenance fluid” and “replacement fluid.” Maintenance is used to replace insensible loss, about 30 mL per hour. This is usually provided as 5% dextrose and water. Urine output and any nasogastric fluid losses are replaced by replacement fluid using half-normal saline because the urine sodium concentration in the early postoperative period is usually 60 to 80 mEq/L. One protocol is to replace all of the initial 200 mL, and then to replace 50% of any volume greater than 200 mL. If the patient is hypovolemic, a greater volume of the urine is replaced, and occasionally if the urine output is low, an additional 500 to 1000 mL of isotonic saline is given as a bolus. Where necessary, potassium, bicarbonate, or calcium replacement should be given in a separate infusion. Potassium replacement should be gradual in oliguric patients, and even some patients with good urine output may not excrete significant amounts of potassium. Serum electrolytes should be ordered at least every 6 hours and more frequently if there are clinical indications to do so such as a very high urine output, or if potassium is being replaced.

Hemodynamic Evaluation

Frequent hemodynamic evaluation is important because an adequate blood pressure and volume status is necessary to establish good graft function. The adequacy of urine output has to be assessed in the context of these two parameters. This may require the use of central venous pressure or a pulmonary pressure or pulmonary wedge pressure measurement. However, for most stable patients, this is not necessary, and a simple regular clinical assessment should be sufficient. Many patients are hypertensive after surgery. This may resolve spontaneously or with adequate pain control, and over-aggressive intervention may lead to the pressure falling too low, increasing the risk for acute tubular necrosis (ATN) and delayed graft function (DGF). In the acute setting, a mildly elevated blood pressure (systolic pressure < 180 mm Hg) is acceptable because blood flow to the newly transplanted organ is dependant on an adequate mean systemic blood pressure. Intravenous hypotensive agents such as labetalol or hydralazine can be used, or if the patient is able to take oral medications, one can use drugs such as

clonidine and nifedipine. Unless these are used deliberately to affect calcineurin inhibitor (CNI) concentrations, both diltiazem and verapamil should be avoided because of their potential interactions that increase CNI concentrations.

Assessment and Management of Urine Output

It is a good idea to warn patients before surgery that their urine output after the operation may vary widely. Knowledge of the patient's pretransplantation urine output is important because those receiving preemptive transplants, and even some dialysis patients, may have daily urine volumes of 1500 to 2000 mL, and this urine from the native kidneys must be accounted for in assessing post-transplantation urine output. In most patients who receive living donor

---

transplants, urine output is quite high, partly because of their relatively hypervolemic state, and also because of the diuretic effects of an elevated urea nitrogen and of mannitol if this is used intraoperatively. In patients who receive a deceased donor organ, and who had minimal or no urine output before surgery, urine volumes may range from complete anuria, through various degrees of oliguria, to polyuria with very high hourly urine volumes. The use of furosemide, dopamine, or fenoldopam infusions postoperatively is routine practice in some programs, although their benefit has been hard to prove.

In anuric patients or those with a low urine output, a Doppler ultrasound may be ordered in the in the recovery room to assess the blood supply to the newly transplanted kidney (Fig. 9.1). The urgency with which the ultrasound is performed depends somewhat on whether oliguria is anticipated. Recipients of a living donor transplant are *always* anticipated to have a brisk urine output, and oliguria must be managed in an emergent fashion. If DGF is anticipated, it is reasonable to delay imaging studies. Imaging studies also serve to establish that there is no evidence of ureteric obstruction or a urine leak, although this is usually made obvious by the presence of urine flowing out through the perinephric drain, confirmed by an elevated creatinine concentration in that fluid. The routine use of a double-J stent from the urinary pelvis to the bladder makes ureteric obstruction uncommon. We also recommend an ultrasound for any patient who had a significant preoperative urine output. It is possible that even with the most carefully placed allografts, blood supply may be compromised as the various layers of the incision are closed, and one should not be dissuaded by an overconfident surgical opinion that the blood supply “is fine.” This should be

---

done concurrently with assessment of volume status and patency of the bladder catheter. If the blood supply is compromised, this is a surgical emergency, and the patient should be returned immediately to the operating room. If the Doppler study is inconclusive, an isotopic study using diethylene pentaacetic acid (DTPA) or a MAG3 renal scan can be used to further define any abnormalities of flow, obstruction, or a

urinary leak (see Chapter 13).

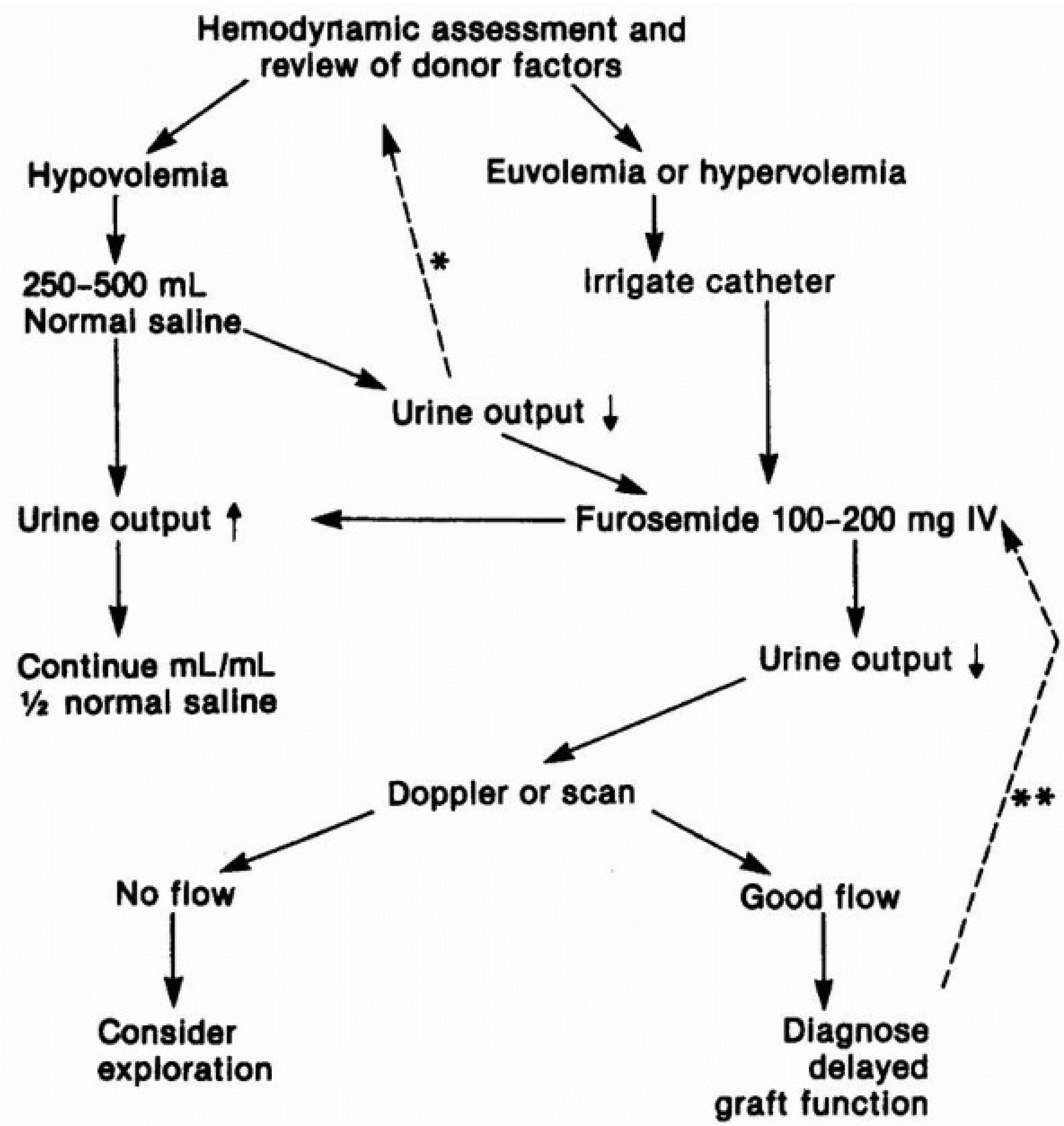


FIGURE 9.1 Algorithmic approach to post-transplantation oliguria. *The volume challenge can be repeated, but only after careful reassessment of the volume status and fluid balance. **Repeated doses of intravenous furosemide “drips” may be valuable in patients whose urine output fluctuates. Persistent oliguria usually does not respond to a repeat dose.

When the urine volume is low, less than 50 mL per hour, or in the presence of anuria, additional initial evaluation includes careful assessment of the patient's volume status and fluid balance, and confirmation that the bladder catheter is not obstructed, by irrigating it gently to avoid excessive pressure on the newly fashioned ureteric anastomosis. If there are blood clots affecting the patency of the catheter, gentle

irrigation may be continued to flush them from the bladder. If this fails, the catheter should be replaced. If the patient appears hypovolemic, a bolus of isotonic saline should be ordered, and when the patient's volume status is acceptable, or when initial assessment confirmed adequate hydration, a 100- to 200-mg dose of furosemide is given intravenously. If there is no response at this stage, there is little value obtained from repeated doses of diuretic, and the patient should remain on the standard fluid replacement orders. In the rare instance of overzealous fluid replacement, it will be necessary to use dialysis to remove sufficient fluid to correct edema, hypoxia, or congestive heart failure. Here, too, care should be taken to maintain an adequate mean systemic blood pressure at all times, to avoid adding to the degree of ATN.

Postoperative Bleeding

Any combination of the triad of hypotension, a decreasing hematocrit, and pain should raise the suspicion of significant postoperative bleeding. The perinephric drain may fill with blood, or there may be a visible or palpable hematoma. If the hematoma is contained, the buildup of pressure will usually be sufficient to stop further bleeding. If this hematoma appears to be placing pressure on the ureter or vascular bundle, it may be prudent to evacuate it to lessen the risk for ureteric or vascular necrosis. If bleeding continues, and especially if it is not possible to maintain the blood pressure with intravenous fluids or blood replacement, exploration may be required to try to find the source of persistent bleeding. Occasionally, the bleeding is retroperitoneal, and this may be associated with significant pain. In patients with coronary artery disease and in diabetic and older recipients, it is important to maintain a hemoglobin above 10 g/dL.

Postoperative Dialysis

It is usually possible to dialyze patients preoperatively to reduce the requirement for postoperative dialysis. Postoperatively, if the serum potassium concentration is elevated or if the patient is compromised by overhydration, dialysis should be performed to correct this. Except in emergencies, it is possible to use both hemodialysis and peritoneal dialysis if the peritoneal dialysis catheter is still in place. Some centers now routinely remove peritoneal dialysis catheters in all living donor transplant recipients and in those deceased donor recipients in whom it is thought that DGF is unlikely to occur. If hemodialysis is used, the blood pressure must be maintained at adequate levels, and no heparin should be used. In the case of peritoneal dialysis, the volumes used for each cycle should be reduced to about 500 mL because larger volumes may be associated with significant pain.

THE FIRST POSTOPERATIVE WEEK

In most transplantation centers, patients are discharged before the end of the first week. This period is usually one of an improvement in allograft function. Immunosuppressive therapy is adjusted, as described in Chapter 5, and

attention is paid to the control of hypertension and hyperglycemia. As soon as possible, patients should be advised to sit out of bed and to take short walks.

Although the urine output is still measured, the frequency of measurement may be reduced and patients switched to a standard intravenous fluid regimen rather than adherence to replacing the urine output. As soon as patients are able to take in sufficient fluid by mouth, the intravenous fluids may be discontinued. Any significant decrease in urine output should be investigated and managed along similar lines to the recommendations on the immediate postoperative day. The bladder catheter is usually retained for 3 to 4 days, although some surgeons remove it earlier. After it has been removed, patients should be advised to attempt to void on a frequent basis even when they do not feel an urgency to do so. Patients who have been anuric for many years may have quite small contracted bladders and may find that they have to void frequently. This may alarm them, and they should be reassured that this will correct itself quickly as the bladder starts to stretch and accommodate. In older men who may have undiagnosed prostatic disease, and in patients at risk for neurogenic bladder dysfunction, a postvoid residual urine volume should be assessed, and if this is greater than 100 mL, the catheter should be replaced. If this problem persists, these patients will require training in self-catheterization either during this admission or later as an outpatient. In older men, an α-blocking drug, such as terazosin, doxazosin, or tamsulosin, should be started before re-removal of the catheter to facilitate voiding at the next trial. The perinephric drain should be retained until after the bladder catheter is removed, and even then kept in place if more than 100 mL per day of fluid is drained through it. This can be left in at discharge and removed in the clinic.

Most patients recover bowel function rapidly over the first 2 days and may be advanced from a liquid to a solid diet. Occasional patients have a more prolonged ileus, and this may be associated with marked bowel distention. There is the possibility of them developing Ogilvie syndrome, a dilated cecum, with a significant risk for perforation. If this occurs, passing a rectal tube may decompress it, but some cases require preemptive surgical intervention. Postoperative incisional pain is managed initially with opiates, and patients should be transitioned to less constipating analgesics as tolerated. The sudden onset of more severe pain, or pain that appears to be aggravated by voiding, suggests the possibility of a urine leak but may also be caused by the development of a new hematoma. Although it is now rare for rejection to cause pain, this also has to be considered in the differential. Fevers are not uncommon and not infrequently caused by atelectasis of the lung. If they persist, they may indicate rejection.

Urine Leak

Urine leaks usually occur at the ureteric anastomosis, most frequently in the first 72 hours, and their management depends on local surgical practice. In cases in which

there is both a perinephric drain and a double-J stent in place, in addition to a bladder catheter, it is reasonable not to intervene except by keeping all of these in place until the leak has healed. A voiding cystogram should be performed to document the leak. If there is no drain, one should be placed percutaneously to drain the urine. It is occasionally necessary to place a percutaneous nephrostomy tube to divert the urine and facilitate healing. This also allows for the performance of an anterograde study of the ureter to better delineate the site of the leak and to exclude ureteric stricture formation. These drains and other tubes are left in place until the leak appears to have healed by virtue of the fact that all the urine is draining through the bladder, at which time the absence of a leak is confirmed by a cystogram. If the leak persists, or if it is considered unlikely to heal, then re-exploration is indicated to reimplant the ureter.

Allograft Function

The recovery of the transplanted kidney dictates much of the early management. If the kidney is not functioning well enough to maintain an acceptable volume and solute homeostasis, intermittent dialysis will be required until sufficient function has recovered. Almost all recipients of a living donor kidney, and about half of recipients of a deceased donor kidney, will rapidly develop excellent kidney function, and the serum creatinine concentration will decline to normal range. These patients do not require any further imaging studies except in the circumstances of altered kidney function described previously. The creatinine and the urine output can be used as measures of changes in kidney function and as markers of the development of new problems, such as rejection, problems with blood flow to the kidney, or obstruction to urine flow. Deterioration in function may result from CNI toxicity, rejection, or development of other pathologic events such as a thrombotic microangiopathy (TMA). Most of the remaining patients will have a more gradual decline in kidney function, but unless it is thought that the rate of improvement in function is slower than expected (the term *slow graft function*, or SGF, is sometimes used), these patients can be managed in the same way. If the creatinine plateaus, or if it increases, the CNI level should be adjusted if it is elevated; and if the creatinine remains high, an ultrasound and a biopsy should be performed. In patients with DGF, in the event that there are no markers that suggest the onset of rejection or other problems (Table 9.2), it is recommended that they have an ultrasound and biopsy every 7 to 10 days, until there is evidence of an improvement in function. It is not necessary that they remain in the hospital for dialysis or biopsy because these can be arranged in the outpatient setting.

Acute Tubular Necrosis

Most cases of DGF are a consequence of ATN. Other causes of DGF include accelerated cellular or humoral rejection, vascular insufficiency, or an undiagnosed obstruction or a urinary leak. There have been reports of the ureter being mistakenly anastomosed to the peritoneum, and in anuric patients who develop abdominal distention and

“ascites,” this needs to be considered. ATN is an ischemic injury that results from acute kidney injury (AKI), which occurs in the donor before the removal of the organs, the impact of ischemia during the period the organ is maintained in preservation fluid, a prolonged warm ischemia time during surgery, reperfusion injury, and any episodes of hypotension following implantation. Animal models have demonstrated that brain injury leads to the release of inflammatory cytokines that cause injury to the

endothelium and not infrequently some degree of TMA. The organ is almost always affected to some extent by ischemia-reperfusion injury, which occurs when oxygen is again available to the tissues, and results from the high concentration of oxygen free radicals that develop during anaerobic metabolism. These include hydrogen peroxide and superoxide anion that cause lipid peroxidation of the cell membranes. It is not infrequent for the newly implanted kidney to initially diurese well, followed by the onset of oliguria as the kidney becomes more swollen and inflamed after reperfusion. There are a number of experimental agents being studied to ameliorate this process, some focused on increasing the production of heat shock protein, heme oxygernase-1, a molecule that appears to protect against this injury.

TABLE 9.2 Differential Diagnosis of Delayed Graft Function

Acute tabular necrosis
Intravascular volume contraction
Arterial occlusion
Venous thrombosis
Ureteric obstruction

Catheter obstruction
Urine leak
Hyperacute rejection
Nephrotoxicity
Thrombotic microangiopathy

ATN is primarily a clinical diagnosis and can be confirmed by biopsy. On occasion, an ATN-like picture can develop both clinically and histologically in patients with C4d +ve antibody-mediated humoral rejection (see Chapter 14). Allograft ATN is similar to ATN in native AKI, with a low glomerular filtration rate (GFR), cellular debris causing tubular obstruction, and increased interstitial pressure from leakage of tubular fluid through the damaged tubules. Renal blood flow is well preserved, with dissociation between flow and excretory function. A Doppler ultrasound may show an elevated resistive index (RI) of greater than 80% (see Chapter 13).

In the presence of ATN, it is important to maintain adequate immunosuppression. It is thought that endothelial injury upregulates and exposes donor histocompatibility antigens, adhesion molecules, and costimulatory molecules, heightening the risk for acute rejection. Some programs avoid introducing CNI in this setting, choosing rather to use antibody induction therapy, although the data supporting this is not that conclusive. However, this strategy has two benefits. The first is that it removes the additive injury that may result from CNI exposure, and the second benefit is that it reduces the risk for rejection at this time of heightened immunogenicity. Sirolimus is also avoided in this setting because it is known to prolong the recovery from ATN. There is considerable evidence that the development of ATN results not only in AKI, but that it also affects long-term graft survival by starting a cycle of low-grade inflammation and fibrosis. The factors implicated in this pathway of injury, inflammation, immune activation, and fibrosis include nitric oxide, epidermal growth factor, and transforming growth factor-ß.

The prevention of ATN starts with the care of the donor, avoiding hypotension and dehydration. Cold ischemia time should be kept as short as possible. During surgery, good hemodynamic management is crucial, and as described previously, postoperative care includes attention to volume status and the maintenance of an adequate blood pressure. ATN is unusual in kidneys transplanted from living donors, emphasizing the impact of all the factors that increase the risk for it developing. The use of extended criteria donor kidneys (ECDs) and donors after cardiac death (DCDs) may increase the incidence of ATN. This has a potential impact on the need for dialysis, the need for radiologic studies and biopsies, the incidence of acute rejection, long-term graft function, and the cost of transplantation. However, some programs have reported that the incidence of ATN and DGF is no greater in kidneys in these categories provided that the donor and transplant recipient management is performed with extreme care.

The impact of DGF on long-term graft survival has been examined in a number of studies that have reported quite different outcomes. Some suggest little impact, whereas others have reported a reduction in 1-year graft survival, a surrogate for long-term survival, by as much as 20%. The definitions used for DGF have varied considerably, and this makes comparison of these studies difficult. Raw DGF data do not adequately describe the extent to which different

---

study populations had significant ATN. It does appear that long-term outcomes are not significantly changed if rejection is prevented in kidneys affected by ATN. This emphasizes the importance of maintaining adequate immunosuppression and of repeating biopsies every 7 to 10 days in these patients.

In addition to the clinical significance of DGF, the diagnosis has financial and programmatic significance. From the previous description, it is clear that DGF is resource demanding. It is expensive and affects the financial viability of transplantation programs. Its avoidance has important implications over and above the strictly clinical ones. Some programs may avoid accepting potentially viable organs from ECD donors for fear of endangering transplantation center finances (see Chapter 20).

Allograft Rejection

Accelerated Acute Rejection

Accelerated acute rejection was described before the availability of assays for preformed cytotoxic antibodies and before there were adequate crossmatch techniques that exclude immunologically incompatible donor-recipient pairs (see Chapter 3). It is caused by prior sensitization, predominantly from blood transfusion, which results in the development of preformed cytotoxic antibodies against human leucocyte antigens. This is a form of humoral vascular rejection that can occur immediately after reperfusion of the transplant, called *hyperacute rejection*, or it may take a number of

days, called *delayed hyperacute rejection*. This is now a rare event, but in patients with high concentrations of preformed antibodies must still be a considered in the differential diagnosis of early graft dysfunction. Compared with vascular thrombosis of the allograft, these patients often are febrile, and the kidney may be swollen and tender and very firm to palpation. Doppler ultrasound will show impaired flow, and nuclear imaging studies will show both impaired flow and excretion (see Chapter 13). In this setting, surgical exploration is indicated to exclude a vascular catastrophe and to obtain a biopsy of the kidney.

Early Cell-Mediated Rejection

It is unusual for classically described acute cellular rejection to occur before the end of the first week, although some have reported cellular infiltrates in the interstitium and subendothelial sites earlier than this. Interpretation of these early biopsies may be confused by the inflammatory response to ischemia-reperfusion injury. When the recipient has received recent blood transfusions, particularly if these were of donor-derived blood, early acute cellular rejection may be more common. Episodes of cell-mediated rejection most commonly present as an asymptomatic rise in the serum creatinine or in the failure of the serum creatinine to decrease below an elevated level. Classic accompaniments of acute rejection, fever, graft tenderness, oliguria, hypertension, and volume expansion may be absent or mild. Renal perfusion is affected less in this form of rejection, particularly if there is also a component of vascular rejection. This pattern of rejection is diagnosed by biopsy. The pathology and treatment are described in Chapters 5 and 14.

Antibody-Mediated Rejection

The diagnosis of antibody-mediated humoral rejection was not feasible until the demonstration that peritubular capillary staining for a complement component, C4d, was a marker for this form of rejection (see Chapter 14). The histologic appearance may otherwise appear as ATN, and there may be features of concomitant cellular rejection. This form of rejection usually occurs early after

---

transplantation with an elevation in the serum creatinine. It most frequently, but not invariably, occurs in the setting of preexisting sensitization. It is useful to repeat the cytotoxic crossmatch if possible and to measure donor-specific antibodies in the recipient. As pathologists have become more adept at diagnosing this form of rejection, it is missed less frequently, but in persistent ATN, it is worth making extra efforts to stain for C4d positivity. It does not respond to the usual treatments for cell-mediated rejection and is most responsive to treatment with intravenous human immune globulin. In addition, plasma exchange may be used to lower the levels of cytotoxic antibodies, and there have also been reports of the use of rituximab, the anti-CD20 B-cell antibody (see Chapter 5).

Nonimmunologic Causes of Graft Dysfunction

There are a number of other causes of real or apparent deterioration in graft function in this first week. These include arterial or venous compromise, renal vein thrombosis, ureteric obstruction, a urinary leak, and necrosis of the ureter. Vascular complications and obstruction are usually asymptomatic, but a urinary leak is frequently accompanied by excruciating pain. There may be drainage of fluid through the incision of the perinephric drain has already been removed. The investigation of these was described earlier in this chapter. CNI toxicity is another cause of an elevation in the creatinine level, and it is not infrequent for the creatinine to decrease low initially, and then to rise over a number of days as the effect of the CNI takes effect. This toxicity includes a direct effect on the tubules and also vasoconstriction of the afferent arteriolar arteries leading to decreased filtration as a consequence of a lower intraglomerular pressure (see Chapter 5, Fig. 5.2). Physicians must balance the requirement for adequate early exposure to CNI to prevent rejection against the possibility of CNI toxicity. In most cases, patients will have an allograft biopsy, and in the absence of evidence for acute rejection, it is reasonable to gradually lower the CNI doses to achieve a reduction in the measured levels. Patients with an increased risk for thrombosis, such as those with the anticardiolipin antibody syndrome, those with systemic lupus erythematosus (most frequent), or with a factor V Leiden deficiency should have been diagnosed before transplantation and placed on heparin anticoagulation immediately after transplantation (see Chapter 8). Dehydration may occur from inadequate fluid intake or from excessive diuresis either from the effect of prescribed diuretics or from uncontrolled hyperglycemia or hypercalcemia, and this may lead to deterioration in kidney function. The early use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) may rarely cause an elevation in the creatinine. In the past, there was reluctance to use these in the early postoperative period, but provided one is aware of their potential to cause renal dysfunction and hyperkalemia, there is no reason these should not be prescribed as early as the first week after transplantation. Renal artery stenosis (RAS) may amplify the effect of CNI toxicity, dehydration, and ACEI and ARB use. If the creatinine level fluctuates, RAS should be excluded by Doppler ultrasound. Another source of this problem is more proximal stenosis of the iliac artery, particularly in diabetic patients and others with diffuse vascular disease, a phenomenon sometimes referred to as *pseudo renal artery stenosis*. When evaluating the renal artery, always request the radiologist to also evaluate the iliac artery.

Thrombotic Microangiopathy

Those patients known to have a TMA from thrombotic thrombocytopenic purpura (TTP) or the hemolytic uremic syndrome (HUS) are at increased risk for developing a TMA after transplantation (see Chapter 7). Both CNIs have been

associated with the development of TMA. It may occur quite rapidly after the introduction of CNI or take several months to develop. Sirolimus has been implicated as a cause of TMA, and TMA has been described in patients receiving OKT3. The pathogenesis of TMA and the morphologic findings are described elsewhere (see Chapter 14). The usual extrarenal manifestations of TTP may not be present because the condition can be limited to the allograft with no decrease in the platelet count, distorted erythrocytes, or elevation in the lactate dehydrogenase (LDH) levels. TMA has been reported to occur in about 15% of transplant recipients, with about 3% showing evidence of TTP. TMA may accompany antibody-mediated rejection, and a biopsy specimen that contains microthrombi should be evaluated for C4d staining. Treatment includes discontinuing the CNI or sirolimus, substituting other immunosuppression, and plasmapheresis.

Antiglomerular Basement Antibody Disease

When antiglomerular basement membrane (anti-GBM) disease was the cause of the initial kidney disease, it is rare for it to reoccur in the allograft provided sufficient time has elapsed since the initial disease presented and provided the concentration of anti-GBM antibodies is unmeasurable. However, patients with Alport syndrome, in which the recipient's GBM is abnormal, are at risk for developing anti-GBM disease early after transplantation when their immune system is first exposed to the normal GBM in the donor allograft. This may occur within the first week and be misdiagnosed as acute rejection. Treatment includes plasmapheresis, with or without cyclophosphamide. As with anti-GBMD in the native kidneys, early diagnosis and treatment are important because after patients are on dialysis, it is difficult to reverse the process sufficiently to regain kidney function.

Medical Management in the First Week

Hypertension, hyperglycemia, and electrolyte abnormalities all require compulsive attention in the first week. Hypercalcemia and hypocalcemia can both occur quite rapidly and should be treated appropriately. The dihydropyridine calcium channel blockers are a good choice to control early postoperative hypertension, as are clonidine and hydralazine. Some patients develop accelerated hypertension and may require multiple agents to control this adequately. It has rarely been necessary to perform an urgent bilateral native nephrectomy in patients with resistant severe hypertension. The blood pressure should always be lowered gradually to avoid causing hypotension. Many patients, particularly those with an autonomic neuropathy and supine hypertension, may have elevated blood pressures when lying flat. It is also best to measure the sitting and standing pressures to avoid overtreatment and postural orthostatic hypotension. This is another reason to encourage patients to sit out of bed as much as possible and to walk regularly. The calcium channel blockers may cause dizziness without causing hypotension. They may also aggravate edema formation. ACEI and ARB may be introduced early. At this time, the creatinine and potassium levels are measured

frequently, and any unwelcome changes are identified and evaluated rapidly.

Hyperglycemia should be controlled in the immediate postoperative period by an insulin infusion. In patients at risk for developing new-onset diabetes after transplantation (NODAT), and in those with type 2 diabetes who are not currently on insulin, consideration should be given to using cyclosporine as the CNI because it is less diabetogenic than tacrolimus (see Chapter 5). In addition, steroid exposure should be minimized, with possible discontinuation of prednisone within the first few days in patients considered to be at low risk for

---

rejection. Once patients are eating, they should be transitioned from intravenous insulin to a subcutaneous regimen. Patients already using an insulin pump can restart this. They should be informed that their insulin requirements will initially be higher than before the transplantation and that they will change as the steroid effect is reduced. Newly hyperglycemic patients should be started on a sliding scale using NovoLog insulin if it is expected that they will no longer be hyperglycemic as the steroid effect wanes. For diabetic patients on a regimen that includes a longer-acting basal insulin and preprandial NovoLog insulin, a correction scale using NovoLog insulin should be used. During the first post-transplantation week, all hyperglycemic patients, including those previously diabetic, should receive teaching from a diabetic educator, emphasizing the effects of the immunosuppression, of missing meals, and of exercise on the use of insulin. If the transplantation team does not feel competent to manage the diabetes, an endocrinology consult should be requested. The endocrinologist needs to be made aware that the food intake of these patients will vary considerably in the early weeks because many of the drugs affect their appetite and may cause nausea, and of the intended changes in the immunosuppression because these have the most profound effect on the serum glucose levels. It is initially easier to treat patients with twice-daily NPH insulin and to switch to a longer-acting insulin such as Lantus or glargine only after the patient is on a more stable regimen and is eating regularly.

Patients may develop significant fluid retention in the early post-transplantation period. This is both uncomfortable and disturbing because patients see it as a sign that the kidney is not functioning well. While on dialysis, patients may have had an established dry weight lower than would have been the case had they had normal kidney function, and they have to adapt to a more volume-expanded state. It is not infrequent for patients to develop localized edema in the arm as a consequence of the increased venous pressure caused by a large arteriovenous fistula or because of a venous stenosis from a previous temporary dialysis catheter. A Doppler study should be ordered to exclude a venous thrombosis, and the edema should be treated locally if possible by angioplasty of the stenosis. Overaggressive diuresis in this setting may result in an elevation in the creatinine level.

Surgical Incision, Drains, and Stents

Improved surgical techniques and prophylactic antibiotics have made infections and dehiscence of the incision uncommon. Obese patients are at greater risk and should be evaluated frequently. The use of sirolimus, particularly in higher loading doses, may delay wound healing, and some programs now avoid it in the early period. It is not uncommon for serosanguineous fluid to drain through the incision in the first few days. If this increases, fluid should be collected in a syringe and sent for estimation of the creatinine concentration, which can then be compared with that of the serum to exclude a urinary leak. Staples and sutures are removed about 2 weeks after the surgery. The drain, when present, is removed some hours after removal of the bladder catheter, unless it continues to drain more than 100 mL per day. If there is a double-J stent in the ureter, patients should be advised of this, and cystoscopic removal is scheduled at about 3 to 4 weeks.

THE DAY OF DISCHARGE

The first week after the transplantation is overwhelming for most patients. In the short period of 4 to 6 days, they have adjust to their new circumstance and learn as much as possible about their responsibilities after discharge. Family members have to adjust their lives to accommodate the frequent visits to the

transplantation center before and after discharge, and they too have to become involved in post-transplantation care. It is easy to forget that many of the functions performed by highly trained nursing staff, when the initial admission was 3 weeks or longer, are now expected of the “caregiver,” occasionally with help from a home care service. Patients have to learn how to care for themselves—to monitor their blood pressure, temperature, glucose concentrations, and weight. They need to know what symptoms to be aware of (e.g., a decrease in urine output, allograft tenderness or pain) and the why, when, and how of their new medication schedule. The transplantation team should be endlessly patient and understand this enormous new burden. Some patients develop psychological changes in this period from the medications and the stress and anxiety, and help dealing with this must be available. Patients should receive clear instructions, easy to understand medication lists, and a log to record the parameters that the transplantation team will need to follow their progress. All patients, not only those with diabetes, should receive nutritional education before discharge and advice on starting a regular graduated exercise program. A discussion should be had about avoiding any gain in weight because many patients believe this is an inevitable consequence of transplantation. They should be seen by the social worker to resolve any potential problems and by the nurse coordinator and the medical team to discuss their new medications and other post-transplantation issues. They must be made aware of the most common medications that interact with their immunosuppression. Contraceptive advice must be given to women of childbearing age because they may not realize how quickly fertility will be reestablished. They need advice about the risks the medications they are taking pose for a fetus.

It is important to emphasize that although rejection and infections are now infrequent, they still occur and are usually treatable. Readmission to hospital always suggests to patients that things are not going well, and they need to know that most often this is required because it is safer and logistically easier for the patient and the team. It is usual to tell patients that a 3-month leave from work is legitimate, but that if they feel well enough, they may return to work far sooner at the discretion of the physicians monitoring their progress.

FROM DISCHARGE TO THE END OF THE FIRST 3 MONTHS

During the period from discharge to the end of the first 3 months after transplantation, there remains the risk for significant complications, but for most patients, this is a time for establishment of normal renal function, with a few ups and downs, and for a routine that should be emphasized to reduce the risk for later nonadherence to the medication regimen required, and for fostering a healthy lifestyle, good diet, and regular exercise.

Most patients are now discharged at or before the end of the first week. There are logistical issues to address because patients will have to attend clinic 2 or 3 times a week for the first month and then weekly for the next month. Sometime between the 8th and 12th weeks, their care will be transitioned to their local physicians. The extent to which the transplantation center will remain responsible for aspects of their care and adjustment of their immunosuppression varies from program to program, and patients have to know who is taking responsibility for which aspects of their care: themselves, the local physician, or the transplantation center.

Clinical Course

By the second week after transplantation, most patients have established good renal function. A few will have prolonged oliguria and will require dialysis between regular visits to a clinic to assess whether this can be discontinued.

They will require the regular surveillance studies and biopsies previously described. For all patients, at each visit, the log should be reviewed. This reinforces the important role they and their families play in their care. The medications should be reviewed and then adjusted according to the findings from the history and physical examination and the blood pressure and glucose records. Ideally, the laboratory results, a urinalysis, fasting chemistry tests, a full blood count, and drug levels from that day are made available to the team members by the time they see the patient. This significantly improves the ability of the physician to make sensible alterations to the medications. The physical examination should, as always, pay close attention to the state of hydration and to the incision and the allograft.

Fever

A low-grade fever is common. Although we still teach patients that a fever may

indicate rejection, this is now a rare manifestation of immune activation, and a fever is most frequently caused by infection of the urine, lungs, or incision. The diagnosis and management of these infections is discussed elsewhere (see Chapter 11). The most common viral infection, cytomegalovirus (CMV), may cause a fever in addition to respiratory or gastrointestinal symptoms. Current practice is to provide prophylaxis to prevent CMV infection, but despite this, about 20% of patients still require treatment. This does occur during the first 3 months and is common in the month after prophylaxis is stopped (at either 3, 6, or 12 months). Patients who are seronegative and receive an organ from a seropositive donor are at highest risk, and they should be aware of this risk. All febrile patients should be examined thoroughly, with close attention to the incision, and should have chest radiographs and a urine culture if there is pyuria. If no obvious source is found, one should not forget infection of the arteriovenous dialysis access, sinuses, teeth, or perineum. If the peritoneal catheter or percutaneous hemodialysis catheter is still present, peritoneal fluid or blood cultures should be sent for culture.

Elevation of the Serum Creatinine Concentration

Patients soon learn that the creatinine level is a major focus of each clinic visit. It is important for them to get into the habit of knowing their own results and what is considered a significant change so they can discuss this with their local doctor, after their care has been transitioned, if it seems that a change is not being adequately addressed. Programs vary in their “tolerance” for increases in the creatinine level, or indeed its failure to continue decreases to an acceptable level. It is often said that an increase of more than 25% from the previous level is significant enough to warrant investigation, but many programs are more aggressive than this and will perform a biopsy with lesser elevations. The procedure has a low risk of complications and obviates treating patients empirically for rejection.

Biopsies are nearly always performed in the outpatient setting. The potential side effects of empiric therapy probably carry more risk than does a biopsy. Frequent measurement of the creatinine level will establish the baseline range for each patient. The most frequent cause of an elevated level is relative CNI toxicity. After this has been addressed, the next step is to exclude structural problems of either the blood vessels or the drainage system by Doppler ultrasound (see Chapter 13) and then Doppler ultrasound, and then to move directly to a biopsy if none is present. Patients may be on aspirin therapy, and the risk for bleeding if the biopsy is performed immediately has to be weighed against that of not intervening early if rejection is present. An INR and platelet count should be available. If the creatinine is not rising rapidly, it is possible to wait 48 hours as the CNI is adjusted and the aspirin withheld. Patients receiving clopidogrel (plavix) may need to wait several days before it is safe to perform a biopsy. If obstruction is present, a nephrostomy tube is placed, and the creatinine level is followed serially. If the creatinine level fails to decrease, a biopsy may still be

indicated. The diagnosis of renal artery narrowing by Doppler ultrasound may require further intervention for possible angioplasty.

Cyclosporine and Tacrolimus Concentrations

Therapeutic drug monitoring is used to adjust the dosing of the CNI. Guidelines are discussed in Chapter 5, Part IV. Historically, 12-hour trough concentrations (CO) have been used to monitor both drugs, but more recently, peak 2-hour postdose (C2) monitoring of cyclosporine has been recommended and in most studies has been shown to be superior to CO, except when the protocol required a high CO range. C2 allows more precise dosing and has been shown to reduce the side effects, particularly of hypertension and hyperlipidemia. It should be recalled that CO monitoring for cyclosporine was introduced to prevent toxicity rather than to improve efficacy and that the correlation of CO and drug exposure is poor. Many studies have shown that there is a significant overlap between concentrations at which both toxicity or rejection can occur, and rejection should be considered even in patients in the high range, and toxicity even when the level seems low. CNI toxicity includes intense afferent arteriolar vasoconstriction, reduction of glomerular capillary pressure, and direct cytotoxic effects on the tubular cells. If it is thought that graft dysfunction is caused by CNI toxicity, the dose should be reduced and the patient reevaluated within 48 hours because it takes about this time for the effect of the CNI to reverse. If the clinical picture is not clear, it is better to obtain a biopsy because, in a time when rejection is infrequent, we often diagnose it in the context of relative underdosing of the CNI in an attempt to reverse toxicity. A biopsy also allows the diagnosis of other, less expected causes of an elevation of the serum creatinine, such as polyomavirus infection, TMA, early post-transplantation lymphoma, humoral rejection, and pyelonephritis, and recurrent kidney disease, particularly focal sclerosing glomerulosclerosis (FSGS), or the onset of anti-GBM disease in patients with Alport syndrome (see Chapter 14).

Graft Tenderness

As is the case for a fever, graft tenderness used to be a hallmark of acute rejection, but with current immunosuppression, this is an unlikely cause. In the initial period, the site of the incision may be tender, but this resolves quickly unless there is a hematoma or infection. If the graft then becomes tender or enlarged with a rising creatinine level infection, obstruction, bleeding, and rejection have to be considered. An ultrasound will exclude a structural cause, a urine culture should be obtained, and if uncertainty persists, a renal biopsy is performed. Viral infections and CNI toxicity are not associated with pain or swelling.

Alternative Techniques to Diagnose Rejection

The realization that an increase in the creatinine level only occurs when rejection has

already caused significant damage to the allograft has led to many attempts to develop strategies or tests to identify rejection before the creatinine starts to rise. These include various types of immune monitoring and the use of regularly scheduled protocol biopsies performed irrespective of any change in kidney function.

Immune Monitoring

Highly sensitive and specific tests that predict rejection are not yet available, but should they be developed, it might be possible to treat patients without the need to perform a biopsy. Unfortunately, even if tests are developed that predict a particular form of rejection, it is unlikely that they will predict all types of rejection, and a biopsy may still be necessary to better define the treatment required. Tests currently under study include urine and serum perforin and granzyme concentrations that appear to have some predictive value, but because rejection can still occur in the absence of an elevation, they may remain ancillary rather than definitive tests. A promising development is the finding that micro RNA expression patterns may serve as biomarkers of human renal allograft status. Monitoring of donor-specific antibody is also used, but this may have more value in the long-term management than in the prediction of acute rejection.

Protocol Biopsies

At a time when the reported incidence of acute rejection has decreased to about 10% or less at many centers, there is an increased interest in the benefit of performing protocol biopsies to identify patients with inflammation insufficient to affect the creatinine level, but with potential implications for the long-term function of the allograft. The number of biopsies done for cause at any center affects this analysis because the incidence of positive findings will be lower at centers that already have a lower threshold for performing biopsies. The reported incidence of inflammation in these biopsies varies widely, often with a higher incidence of biopsies inadequate to make a diagnosis than those with positive findings, and with poor concurrence between sequential biopsies. Few studies have included follow-up biopsies after patients have or have not been treated, and there are insufficient data on which to base a therapeutic recommendation. In many programs, the incidence of subclinical rejection is so low in patients on either tacrolimus or cyclosporine that it does not warrant continuing to obtain a protocol biopsy in patients not otherwise already studied. For the moment, protocol biopsies may be useful in research settings but have not become clinical standard of practice.

Common Laboratory Abnormalities in the Early Post-transplantation Period

Urinalysis

The performance of a routine urinalysis should be part of every clinic visit. Pyuria usually indicates infection, although it has been associated with rejection. It is more common in patients with an indwelling double-J stent, and this pyuria may be sterile. The requirement for more frequent urine cultures is one of the hidden costs of routine stent placement. Hematuria is common. This may be from continued trivial bleeding at the ureteric anastomosis or from blood clots that are slowly dissolved in the bladder. Patients should be warned that their urine may clear and then again appear bloody as the clots are lysed. The hematuria usually resolves, but in some patients, low levels of microscopic hematuria persist. When there is bleeding into the urine, protein is also invariably present. At this early stage, the most urgent reason for the measurement of proteinuria is in patients with FSGS as their primary diagnosis. FSGS may reoccur early, and if there is proteinuria, the urine protein-to-creatinine ratio should be followed, with any significant increase, an indication for a biopsy.

Potassium

Elevated potassium levels have been a commonly described side effect of CNI from the early use of cyclosporine. The treatment of these moderate degrees of hyperkalemia (in the high 5s) is often more aggressive than is required, and in most patients, intervention beyond dietary restriction is unnecessary. The concomitant presence of an acidosis may add to the hyperkalemia, and this should

---

be corrected by bicarbonate replacement. Other drugs that increase the potassium such as ACEI and ARB, β blockers, and potassium-containing phosphate supplements should be adjusted. If the hyperkalemia is persistent, fludrocortisone is effective, provided the blood pressure and fluid retention are not adversely affected. Oral sodium polystyrene sulfonate (Kayexalate) may also be used.

Hypokalemia is caused by overzealous dietary potassium restriction and diuretic use. Hypomagnesemia is common, and this may potentiate the hypokalemia. Sirolimus may cause hypokalemia.

Calcium, Magnesium, and Phosphate

Hypophosphatemia is common in the early period and is most marked in patients with good allograft function, with 25% or more requiring supplements to bring the phosphate to the normal range. This is usually given in the form of potassium phosphate and may aggravate elevations in the potassium. These supplements may aggravate diarrhea. Patients are often habituated to a low phosphate diet and need encouragement to include phosphate-rich foods in their diet. Dairy products are one such source. Patients also need advice on the avoidance of calcium-containing phosphate binders, and if calcium supplements are prescribed, these should be separated from meals by at least 2

hours. The milder forms of hypercalcemia induced by persistent hyperparathyroidism may be controlled by phosphate supplements. However, if it is more severe, vitamin D supplements can be used or the calcimimetic cinacalcet. If patients were receiving cinacalcet while on dialysis, it may need to be restarted after the transplantation. Occasionally, the degree of hyperparathyroidism and hypercalcemia is severe enough to warrant investigation and parathyroidectomy. CNI use is associated with renal magnesium wasting, and magnesium levels below 1.5 mg/dL are common. Magnesium supplements are often provided but are often ineffective because of the persistent urinary losses.

Hematologic Abnormalities

Most patients are slightly anemic at discharge from the hospital. Many patients are iron deficient at the time of admission, and this may be treated with intravenous iron during the transplantation admission. Many patients absorb oral iron poorly, and intravenous iron infusions may also be prescribed in the outpatient setting. In the perioperative period, erythropoietin administration is likely to be ineffective, but in the clinic, its use will correct the anemia in most patients who are not iron deficient. If anemia persists or if there is a sudden decrease in the hemoglobin, bleeding should be looked for as a cause of the anemia in the gastrointestinal tract and at the surgical site. Where indicated, patients should receive blood transfusions to correct the anemia because this may speed their recovery and reduce the risk for coronary ischemia. Persistent anemia may be a consequence of parvovirus infection (see Chapter 11). ACEI and ARB have been used to correct post-transplantation polycythemia and may be a cause of anemia. Another potential cause of polycythemia is renal artery stenosis, and in polycythemic patients, the iliac and renal arteries should be evaluated even in the absence of an increase in the creatinine level. Patients taking azathioprine almost always have a degree of macrocytosis, and all of the antiproliferative drugs (e.g., sirolimus, azathioprine, and mycophenolic acid) may cause anemia and pancytopenia, although isolated leucopenia or thrombocytopenia may also occur. The more frequent use of alemtuzumab for antibody induction therapy and the use of valganciclovir for CMV prophylaxis have significantly increased the incidence of neutropenia. The dose of valganciclovir should be adjusted for the degree of renal dysfunction. In patients on prednisone-free protocols, neutropenia is more common, and programs that have

---

most experience in this area advise that provided the stable white blood cell count is greater than 1800×10E3/uL and the absolute neutrophil count (ANC) is above 1000 × 10E3/uL, no therapeutic adjustments are indicated. However, if the count is decreasing rapidly, it is prudent to withdraw drugs that affect the bone marrow, including mycophenolic acid, valganciclovir, and sulfamethoxazole. If the ANC is below 500×10E3/uL, subcutaneous neutrophil-stimulating factor should be used.

Transaminitis

Minor fluctuations in the concentrations of the hepatic transaminases are common and probably a manifestation of drug toxicity. These elevations certainly lead to more intervention in terms of alteration in the medications and radiologic studies than is indicated because they almost always return to normal during the first few weeks. Statin drugs, used to control hyperlipidemia, are a common culprit. If there is evidence of more severe hepatic dysfunction, further investigation and referral are indicated. CMV may lead to a transaminitis, and a CMV-DNA polymerase chain reaction study should be obtained if the transaminitis is a new finding and if the concentrations continue to rise.

EARLY POST-TRANSPLANTATION MORTALITY

The overall reported mortality rate in the first year after transplantation is about 5%. Two thirds of the deaths occur within the first 3 months, more frequently in recipients of deceased donor and extended criteria donor kidneys. This may reflect the age of the recipients, less up-to-date cardiovascular studies than for living donor recipients, the nonelective nature of deceased donor transplantation, and the higher rates of rejection treatment with the added cardiovascular and infectious risks. Cardiovascular disease accounts for about 40% of deaths, and infections for another 30%. This emphasizes the importance of optimizing cardiac care by controlling blood pressure, correcting anemia, treating hyperglycemia, and making use of ACEI, β blockers, aspirin, statins, and diuretics. Any symptomatic patients should be referred for urgent cardiac evaluation. If patients are treated for rejection later in the first 3 months, we recommend continuing antiviral and anti-*Pneumocystis* prophylaxis for another 3 months.

REFERRAL BACK TO COMMUNITY CARE

Programs vary greatly with respect to the role of the transplantation program, the community nephrologist, and the primary care physician in long-term patient care. It is critical that the role of each of these sources of care be absolutely clear to the patient. Many patients are referred back to their community nephrologists or their primary source of care toward the end of the third month. It is important that this transition includes clear communication, with transfer of the medical records from the first 3 months, and a discussion about any unusual concerns relating to the patient's care. Community physicians vary with respect to their degree of comfort in taking over all aspects of the patient's care and responsibility for adjusting the immunosuppression. Patients should be seen by their primary care provider monthly at this stage. Follow-up visits at the transplantation center every 3 months until the end of the first year are recommended, and thereafter visits every 6 to 12 months. Patients should also return to the transplantation center for assessment of any significant change in kidney function and of any new comorbidity such as cancer. Some centers maintain control of the immunosuppression dosing for the entire life of the transplant, and if this model is used, it is absolutely necessary for those physicians altering the medications to have a

current list of all other medications the patient is prescribed by their local doctors and knowledge of

all the current medical issues. The community physician should be contacted to discuss any changes made. If this is not the case, there is the danger of drug interactions and other complications, and it is difficult for the community team to adequately care for the patient. If the patient requires an allograft biopsy, it is preferable that this be performed at the transplantation center because of the proximity of pathology expertise and a broad range of therapeutic options.

Selected Readings

Akalin E, Dinavahi R, Friedlander R, et al. Addition of plasmapheresis decreases the incidence of acute antibody mediated rejection in sensitized patients with strong donor-specific antibodies. Clin J Am Soc Nephrol 2008;3:1160-1167.

Anglicheau D, Sharma V, Ding R, et al. MicroRNA expression profiles predictive of human allograft status. Proc Natl Acad Sci USA 2009;106:5330-5335.

Gill JS, Periera BJ. Death in the first year post-transplant: implications for patients on the transplant waiting list. Transplantation 2003;75:113-118.

Humar A, Matas AJ. Surgical complications after kidney transplantation. Semin Dial 2008;18:505-510.

Kurtkoti J, Sakhuja V, Sud K, et al. The utility of 1- and 3-month protocol biopsies on renal allograft function: a randomized controlled study. Am J Transplant 2008;8:317-323.

Lorenz M, Billensteiner E, Bodingbauer M, et al. The effect of ACE inhibitor and angiotensin II blocker therapy on early post-transplant kidney graft function. Am J Kidney Dis 2004;43:1065-1070.

McTaggart RA, Gottlieb D, Brooks J, et al. Sirolimus prolongs recovery from delayed graft function after cadaveric renal transplantation. Am J Transplant 2003;3:416-423.

Montgomery R, Hardy M, Jordan S, et al. Consensus opinion from the antibody working group on the diagnosis, reporting, and risk assessment for antibody-mediated rejection and desensitization protocols. Transplantation 2004;78:181-185.

Pham T, Danovitch GM, Wilkinson A, et al. Inhibitors of ADAMTS 13: a possible etiologic factor in thrombotic microangiopathy in a renal transplant patient. Transplantation 2002;74:1077-1080.

Randhawa P, Brennan D. BK virus infection in transplant recipients: an overview and update. Am J Transplant 2006;6:2000-2005.

Sayegh MH, Colvin RB. Case record of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 8-2003. A 35-year-old man with early dysfunction of a second renal transplant. N Engl J Med 2003;348:1033-1044.

Schwimmer J, Nadasdy T, Spitalnik PF. De novo thrombotic microangiopathy in renal transplant recipients: a comparison of hemolytic uremic syndrome with localized renal thrombotic microangiopathy. Am J Kidney Dis 2003;41:471-479.

Serra A, Wuhrmann C, Wuthrich R, et al. Phosphatemic effect of cinacalcet in kidney transplant recipients with persistent pyperparathyroidism. Am J Kidney Dis 2008;52:1151-1157.

Thaunat O, Legendre C, Morelon E, et al. To biopsy or not to biopsy? Should we screen the histology of stable renal grafts? Transplantation 2007;84:671-676.

10

Long-Term Post-transplantation 10 Management and Complications

Alan Wilkinson

Bertram L. Kasiske

The previous chapter described the care of the patient during the first 3 post-transplantation months. By the end of that period, as patients commence the period of long-term management, the risk for surgical complications, acute rejection, and major infections is diminishing, although these issues continue to be of concern for the rest of the first year, and to a lesser extent for the life of the transplant. By the end of the third month, most patients have had their immunosuppressive doses reduced to the levels that will continue for many years, and the treatment of their hypertension, diabetes mellitus, hyperlipidemia, and other medical issues should be under stable control. Fewer patients now lose their allografts within the first year, and most centers report a 1-year graft survival rate of about 90% to 95%. There has been a gradual improvement in the time it takes for 50% of the grafts to fail, the graft half-life, and because of the thousands of transplantations, performed there are many patients whose grafts have been in place for more than 10 years, and indeed for more than 20 years. The half-life of two-haplotype living donor transplants has been estimated to be more than 20 years, and that of deceased donor grafts more than 11 years. Many of the factors that affect the longevity of the graft are determined by the features of the graft itself and by the early post-transplantation course. A major cause of graft loss is patient death (Figure 10.1), predominantly from cardiovascular disease (CVD). To promote longevity of the graft, the intensive treatment of the medical complications from which transplant patients suffer, particularly those that increase the risk for CVD, are therefore as important as the long-term modification of immunosuppression.

The other major cause of graft loss is chronic allograft failure (CAF), the pathologic features of which are discussed in Chapter 14. In that chapter, an argument is made to avoid the popular term *chronic allograft nephropathy* because, as the graft fails, there is no specific nephropathy as such but rather features of many of the chronic processes that may impair its function (e.g., chronic rejection, chronic calcineurin inhibitor toxicity, hypertension or nephrosclerosis, chronic obstruction, viral infections, and

recurrent diseases). The characteristic histologic features are interstitial fibrosis and tubular atrophy (IFTA). *Chronic rejection* is another term that is often used loosely. The term does not adequately represent etiologic factors in allograft failure that can be considered both immune (alloantigen-dependent) and nonimmune (alloantigen-independent) factors (Figure 10.1). The term *chronic allograft nephropathy* has been removed from the most recent iteration of the Banff classification of renal transplant pathology.

This chapter is divided into two sections. Part I describes the management of medical complications and considers strategies to improve patient and graft outcomes. Part II describes the factors thought to cause CAF and strategies to reduce the rate of loss of kidney function. Inasmuch as CAF typically includes a component of vascular disease, those strategies that reduce CVD almost certainly are beneficial to the graft, as are control of blood pressure, hyperglycemia, and proteinuria. Part II also describes other causes of late graft loss from death after transplantation. Long-term immunosuppressive therapy and the immunosuppressive management of chronic allograft failure are discussed in Chapter 5, Part V; post-transplantation infectious disease is discussed in Chapter 11; post-transplantation liver disease is discussed in Chapter 12; and medication nonadherence is discussed in Chapter 20. Readers are also referred to the American Society of Transplantation's *Guidelines on the Outpatient Surveillance of Renal Allograft Recipients* (See Kasiske and colleague's Selected Readings Part II).

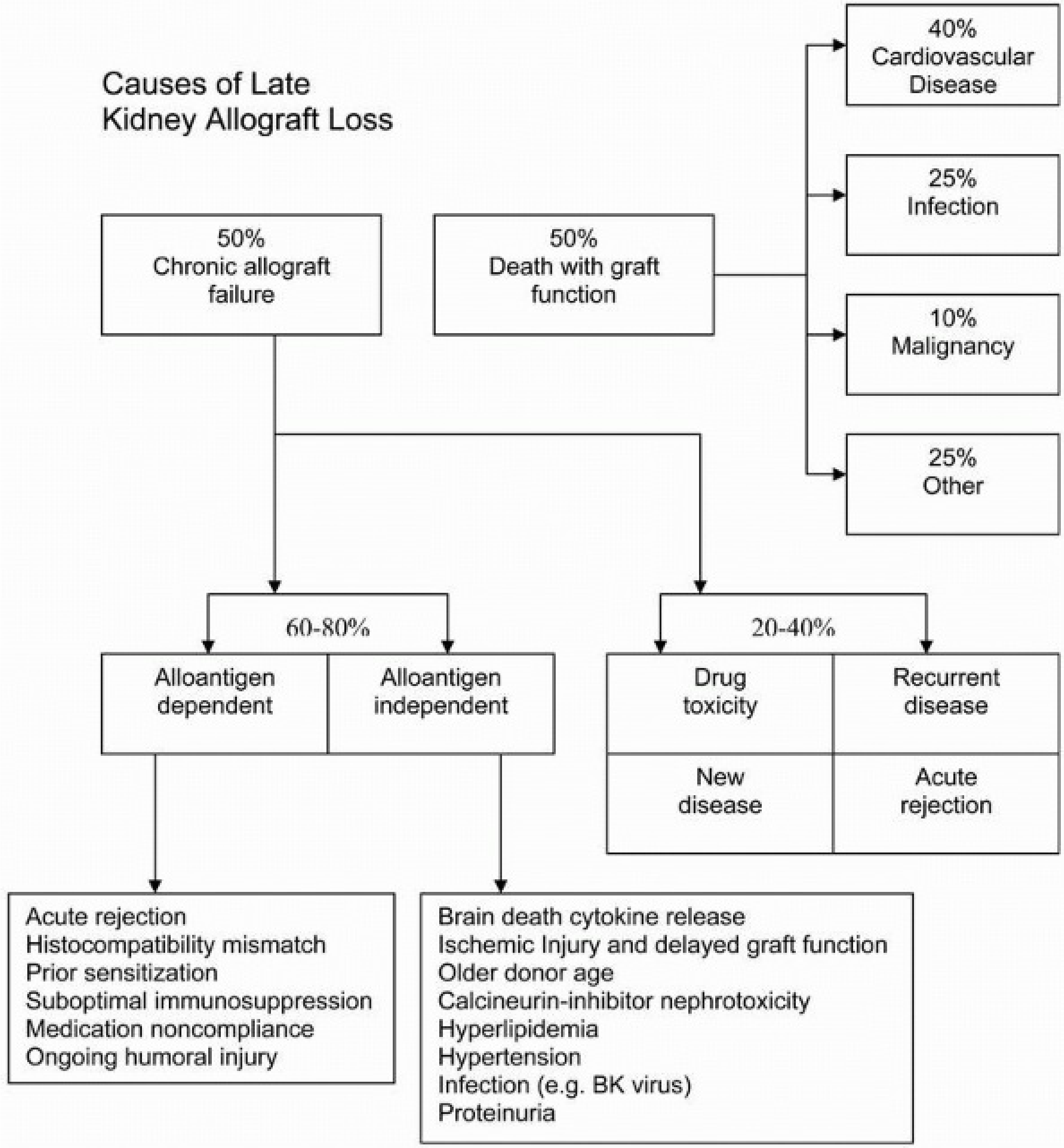


FIGURE 10.1 Causes of late kidney allograft loss.

PART I: MANAGEMENT OF POST-TRANSPLANTATION MEDICAL COMPLICATIONS

Renal transplant recipients should be considered a subset of patients with chronic kidney disease (CKD). A small minority of these patients have normal kidney function, but the glomerular filtration rate (GFR) of the vast majority places them in one of the stages of CKD. Whereas there are factors particular to transplant recipients that may increase the risk for certain diseases and of their complications, in general, guidelines for the management of patients with CKD and those recommended for the general population are applicable to the

management of these patients. A continuous intensive and coordinated approach to the chronic conditions from which they suffer is an important part of their care. The transplantation center, the community physicians, and the patient are all part of the team that has to work to obtain optimal health for these patients and their transplants.

The great disparity between the demand for organs and the supply means that fewer patients than in the past will have successive transplants, and after the first transplant fails, most will return to dialysis for a considerable period of time, if not for the rest of their lives. Both physicians and their patients need to understand this. It should make the prevention of risk factors and adherence to the medication schedule a priority for all these stakeholders. The treatment of chronic conditions can be frustrating and arduous, but the rewards obtained from realizing the benefits of persistence are great. We know from studies in the general population (e.g., in the treatment of hypertension, an established risk factor for stroke and CVD) that even when the evidence is overwhelming that treatment is beneficial, a minority of patients at risk are treated, and a minority of these achieve the targets set in management guidelines. Transplant patients, however, are already well connected to a system that should provide their care, and this should enable more successful prevention strategies. We know the major causes of morbidity and mortality in the late transplant period and in some cases have evidence to suggest effective measures to prevent post-transplantation complications. When evidence is not available from transplant studies, the data from the CKD and general population should be used.

The success of treatment of chronic conditions is enhanced by frequent contact with the patient's physicians. The intensity of care provided to transplant recipients should be tailored to their needs, but in general, it is recommended that after a gradual reduction in the frequency of visits from 2 times per month during the fourth month to 1 time per month at 6 months, this monthly scheduled should be maintained until the end of the first year. For the next year, the visits should be every 1 to 2 months and thereafter every 3 to 4 months as long as the transplant is functioning. Follow-up can occur at the clinic of the transplantation center, with the community nephrologist, or with a community internist or family practitioner with experience in the care of transplant recipients. There should be frequent and open communication between the community physicians and the transplantation center. The transplantation center should remain a source of care and expertise.

The following strategies address the most important management issues in the late transplantation period.

STRATEGY 1: REDUCE IMMUNOSUPPRESSION WHENEVER POSSIBLE

Death is a common cause of renal allograft failure in the late post-transplantation period. The ultimate goal is to have all our patients die with a functioning graft, but not prematurely, as is now too often the case. CVD, cancer, and infection are the

leading causes of death in the late post-transplantation period, and immunosuppression plays a major role in the pathogenesis of each of these complications. Each immunosuppressive agent has both immune and nonimmune toxicity. Immune toxicity is usually nonspecific; that is, immune toxicity is the result of the total amount of all immunosuppression over a given period of time. Immune toxicity can only be avoided if patients became tolerant to their transplanted kidney. Unfortunately, most patients will reject their kidney if immunosuppression is completely withdrawn, and the best we can do is select the minimal amount of immunosuppression that prevents rejection. This minimal amount should ideally be tailored to the needs of specific patients, but we are able to do that only in a crude way.

TABLE 10.1 Tailoring the Amount of Immunosuppression to the Individual

Risk Factor	Patients Who May Need More Immunosuppression	Patients Who May Need Less Immunosuppression
Donor source	Deceased	Living
Major histocompatibility	>0 Mismatches	0 Mismatches
Prior transplant experience	>1, Rejected quickly	0 or 1, Prolonged survival
Age	<18 years old	>60 years old

Race	African American	White
Timing of acute rejection	Late	Early
Severity of acute rejection	Severe, vascular	Mild, cellular
Number of acute rejections	>1	0 or 1

The principal obstacle to reducing the overall amount of immunosuppression is acute rejection. A number of risk factors for acute rejection have been identified (Table 10.1). These risk factors can be taken into account when determining the amount of immunosuppression that may be appropriate for individual patients in the late post-transplantation period. In general, outcomes are better for living donor kidneys. This is especially true for two-haplotypematched living related transplants. Even here one should be careful to provide adequate immunosuppression, and a protocol that uses less exposure to calcineurin inhibitor (CNI) and is more dependent on antiproliferative agents may reduce the long-term risk for CNI toxicity (See Chapter 5, Part IV). For deceased donor kidney recipients, the number of major histocompatibility mismatches is associated with the rate of late allograft failure (see Chapter 3, Figure 3.3). In particular, patients with zero mismatches are at significantly lower risk for late graft failure when compared with patients with as few as one mismatch, and the number of HLA-DR mismatches may predict the incidence of acute rejection after elective withdrawal of a CNI. Patients who have had more than one previous transplant have a higher risk for graft failure. In addition, the chances of such a patient receiving yet another kidney are reduced, making the risk association with reducing immunosuppression higher. Patients younger than 18 years of age have a higher incidence of acute rejection and need more immunosuppression than do patients 30 to 50 years of age (see Chapter 16). On the other hand, elderly patients are more likely to die of complications of immunosuppression than to lose their kidneys to acute rejection, and many transplantation centers attempt to use less immunosuppression in elderly transplant recipients (see Chapter 5). This reduction in immunosuppression should not be too radical. African American patients are at increased risk for late

allograft failure. The reasons for this are probably multiple but include possible differences in immunoreactivity to the graft and poor bioavailability of CNIs. Acute rejection is a strong predictor of outcome, particularly from CAF. However, not all acute rejections lead to graft failure. Characteristics of acute rejection that correlate to increased risk for graft failure and, by inference, increased needs for long-term immunosuppression include late rejections, severe rejections, and multiple acute rejections. All of the above factors can be used to judge the amount of immunosuppression that may be best for individual patients in the late post-transplantation period.

A number of randomized controlled trials have studied the feasibility of electively withdrawing individual immunosuppressive agents in the late post-transplantation period. Withdrawal of both prednisone and cyclosporine has

---

been studied extensively, yet total withdrawal of these agents remains controversial (see Chapter 5, Part IV). Elective cyclosporine withdrawal is associated with about a 10% risk for acute rejection in the months following withdrawal. Most of these rejection episodes can be successfully treated and reversed. Despite this increased risk for rejection, controlled trials with long-term follo-wup have been unable to demonstrate an increased risk for graft failure after cyclosporine withdrawal. In contrast, acute rejection after prednisone withdrawal appears to increase the risk for late allograft failure in randomized controlled trials. Additional studies are warranted to define better circumstances under which immunosuppression withdrawal is advisable. For most patients, low-dose maintenance therapy is safer and less anxiety provoking than total withdrawal of individual agents. Total withdrawal of immunosuppression is not an acceptable or permissible option except in the circumstances of highly experimental tolerance-inducing protocols discussed in Chapters 2 and 5, or in the face of life-threatening infection or malignancy.

In addition to deciding on the minimum amount of immunosuppression needed to prevent acute rejection, physicians and patients must also choose among the most effective, but least toxic, of several different agents. In general, it is prudent to tailor the choice of agents to the risk profile or adverse effects that are most troubling to the individual (Table 10.2). For patients who have severe hyperlipidemia, especially those who are at high risk for CVD, it may be wise to minimize the use of cyclosporine, prednisone, and sirolimus. Each of these drugs causes hyperlipidemia. Switching a patient from cyclosporine to tacrolimus, for example, may reduce low-density lipoprotein cholesterol by the same amount as therapy with an HMG-CoA reductase inhibitor. Similarly, reducing cyclosporine or prednisone dose may help to control blood pressure. Patients with severe tremor will be especially eager to reduce or withdraw tacrolimus or cyclosporine in the late post-transplantation period if this is possible. A significant number of patients receiving cyclosporine develop gum overgrowth. This is made worse by poor dental hygiene and by the concomitant use of calcium antagonists. This reverses if patients are switched to tacrolimus. Similarly, patients with difficult-

to-control diabetes may be good candidates for minimizing doses of prednisone. New-onset diabetes in a patient receiving tacrolimus may respond to switching to cyclosporine. Bone marrow suppression may be an indication for reducing doses of azathioprine, mycophenolic acid, or sirolimus. Patients with marginal renal function may sometimes delay starting dialysis by

decreasing or stopping calcineurin inhibitors. Patients with severe liver disease may benefit from lowering or discontinuing azathioprine. Patients with cosmetic complications may choose to switch calcineurin inhibitors. Allopurinol can dramatically increase blood levels of azathioprine; hence, azathioprine may need to be reduced or discontinued for patients with gout and switched to mycophenolic acid. Tacrolimus may be the better CNI for patients with gout. Finally, many patients cannot afford to pay the high cost of immunosuppression. The use of expensive medications for patients who cannot afford them increases the risk for nonadherence and graft failure. Prednisone and azathioprine are a fraction of the cost of newer immunosuppressive agents and yet may provide adequate immunosuppression for many patients (see Chapter 5).

TABLE 10.2 Tailoring the Type of Immunosuppression to the Individual

Risk Factor or Complication	**Agents to Reduce or Withdraw**
Severe hyperlipidemia	Cyclosporine, prednisone, sirolimus
Severe hypertension	Cyclosporine, prednisone
Severe tremor	Tacrolimus, cyclosporine
Difficult to control diabetes	Prednisone

New-onset diabetes	Tacrolimus, prednisone
Anemia, neutropenia, thrombocytopenia	Azathioprine, mycophenolate mofetil, sirolimus
Severely impaired renal function	Cyclosporine, tacrolimus
Gout requiring allopurinol	Azathioprine, switch from cylosporine to tacrlimus
Cosmetic changes	Switch calcineurin inhibitors
Inability to pay for medications	Simplify regimen, use inexpensive agents

STRATEGY 2: ADOPT STRATEGIES TO PREVENT NONADHERENCE

There are few randomized, controlled trials to suggest how to prevent nonadherence with immunosuppressive medications. On the other hand, a number of observational studies have demonstrated that nonadherence is an important, preventable cause of allograft failure. These same studies have provided clues to preventive measures that are most likely to be effective.

- Minimize the number of daily doses of medication, and whenever possible, use medications that can be dosed once daily.
- Educate patients. In particular, dispel the common misconception that the immunosuppressive effects of medications extend beyond the dosing interval. Patients need to be reminded at every follow-up visit that failure to take medications regularly will eventually result in graft failure.

- Educate and update physicians and medical staff regarding immunosuppressive protocols and individual regimens and the potential for drug interactions (see Chapter 5).
- Help patients to establish a system to remind them to take their medications. Enlist the help of friends, family, and public health aides. Use egg-carton-style pull containers or other mnemonic devices.
- Maintain close contact with patients throughout the late post-transplantation period. Insist that patients have routine follow-up with the transplantation center and make every effort to locate patients who are lost to follow-up. Clinic visits and laboratory checks are a valuable reminder to patients of the importance of taking medications. When negotiating contracts with providers, insist that patients be allowed to follow up with the transplantation center at regular intervals.
- Know whether your patients have trouble paying for their medications. If this is the case, assign someone to help them. Most transplantation programs have found that it is often necessary to have a dedicated social worker or pharmacist available to help patients (see Chapter 20). Be prepared to offer less-expensive alternatives (see Chapter 5).
- Identify patients who are at high risk for nonadherence. Adolescent patients are at increased risk, often because they are fearful of the cosmetic effects of prednisone and cyclosporine. Patients who are poorly educated are also at increased risk for nonadherence. Similarly, low family income is associated with nonadherence. Socioeconomic factors place members of racial minorities at increased risk for nonadherence. Studies show that patients who were nonadherent with medication, diet, and dialysis therapy before transplantation are more likely to be nonadherent after renal transplantation.
- Patients who are at high risk for nonadherence should be targeted with risk factor intervention in much the same way that we target patients who are at high risk for CVD with intensive risk factor management. In both instances, the benefit is likely to be the greatest risk when the risk is the highest.

STRATEGY 3: MONITOR RENAL FUNCTION CLOSELY

Frequent monitoring of renal function in the late post-transplantation period helps to enforce adherence with immunosuppressive medications and provides the only reliable means to detect acute rejection at a time when it may still respond to treatment. A program requiring patients to make certain that serum creatinine is measured regularly and reported to the transplantation center also provides an indirect means for the center to monitor compliance. Patients should also keep a record of their own creatinine values and thereby learn to self-monitor for significant change. Patients who

fail to have their serum creatinine level checked regularly should be contacted and reminded of the importance of close, ongoing follow-up to prevent graft failure. Patients and caregivers should be constantly reminded that acute rejection rarely presents with signs and symptoms in the late post-transplantation period. Although immune monitoring holds promise as a more sophisticated way of recognizing acute rejection before it manifests clinically, the serum creatinine level is currently the only practical tool that can be used to screen for acute rejection in the late post-transplantation period. It is not too much to ask patients to have their serum creatinine level measured regularly in the late post-transplantation period. Measurement of cystatin C may provide a more accurate estimate of GFR in transplant patients than creatinine-based estimations. Cystatin C measurements have yet to be used clinically in a widespread fashion.

At least once a year, and preferably more often, urine should be checked for protein excretion. Persistent proteinuria (i.e., more than 1 g in 24 hours for at least 6 months) is associated with an increased risk for graft failure. Proteinuria can be most reliably detected by either a timed urine collection (which is cumbersome) or a protein-to-creatinine ratio measured in a random “spot” urine sample (which is convenient). Dipstick screening is less reliable because the protein concentration is also dependent on the state of diuresis. There are two reasons why it is important to detect proteinuria.

1. Reducing high levels of proteinuria with an angiotensin-converting enzyme inhibitor (ACEI) or an adrenergic receptor blocker (ARB) may help to reduce levels of serum cholesterol and alleviate coagulation and other metabolic abnormalities associated with nephrotic-range proteinuria.

2. There is growing circumstantial evidence that proteinuria is injurious to the kidney and contributes to the progression of CAF.

STRATEGY 4: MAKE AN ACCURATE PATHOLOGIC DIAGNOSIS OF THE CAUSE OF GRAFT DYSFUNCTION

It is important to establish an accurate pathologic diagnosis in patients with deteriorating graft function. There is evidence to suggest that even low-grade tubulitis, or so-called borderline acute rejection, may increase the risk for CAF (see Chapter 14). The evidence supporting the use of routine protocol biopsies, however, is not strong, and most programs do not perform them unless the patient is engaged in a research protocol. An increased serum creatinine level remains the prompt for biopsy and treatment. However, the message is clear. It is important to have a high level of suspicion for acute rejection and a low threshold for obtaining a renal allograft biopsy. An acute, sustained rise in serum creatinine should prompt immediate evaluation. The strategy of routinely

---

monitoring serum creatinine levels will only be successful if biopsies are obtained

quickly and acute rejection is treated. Such a strategy will also avoid unnecessary intensification of immunosuppression when rejection is not present. Unexpected diagnoses, such as recurrent disease, calcineurin inhibitor toxicity, polyomavirus infection, and post-transplantation lymphoma, may require radically different therapeutic approaches. If a cause of CAF is established, repeated biopsies may be unnecessary because repeated treatment may be unwise (see Chapter 5).

STRATEGY 5: TREAT HYPERLIPIDEMIA AGGRESSIVELY

Hyperlipidemia is common after renal transplantation. Elevations in total cholesterol are almost invariably accompanied by elevations in low-density lipoprotein (LDL) cholesterol. Triglycerides are also frequently elevated. Several studies have found correlations between hyperlipidemia and CVD after renal transplantation. Studies in the general population provide incontrovertible evidence that treatment of elevated LDL reduces the risk for ischemic heart disease events and decreases mortality. Transplant recipients with LDL cholesterol levels higher than 130 mg/dL should be considered for pharmacologic treatment, especially if they have preexisting CVD, diabetes, or other risk factors. Tables 10.3 and 10.4 list recommendations for the primary and secondary prevention of CHD. Recognition of patients with the metabolic syndrome is important early after transplantation so that patients can be targeted for lifestyle modifications and drug therapy.

Reduction of the urine protein excretion with an ACEI or ARB may help to reduce lipid levels for patients with nephrotic-range proteinuria. Reduction or discontinuation of cyclosporine, sirolimus, or prednisone may also help lower lipid levels. Diet is effective in reducing cholesterol and LDL, but the effect is usually modest. A number of studies have shown that HMG-CoA reductase inhibitors are safe and effective in lowering LDL cholesterol after renal transplantation. In the ALERT (Assessment of Lescol in Renal Transplantation; see “Selected Readings”) trial, fluvastatin lowered LDL by 32%, and

---

although there was no significant reduction in the rate of coronary intervention or mortality, the incidence of cardiac deaths and nonfatal myocardial infarction appeared to be reduced. About half of all kidney transplant patients receive these drugs. Plasma levels of HMG-CoA reductase inhibitors are increased in cyclosporine-treated renal transplant recipients, and it is generally prudent to use about half the usually prescribed dose. Patients who still have high LDL cholesterol levels may be candidates for combination therapy. Low-dose bile acid sequestrants can be combined with an HMG-CoA reductase inhibitor. Bile acid sequestrants should probably not be taken at the same time as cyclosporine and should not be used in patients with very high triglyceride levels. Fibric acid analogues, such as gemfibrozil, can also be used in combination with HMG-CoA reductase inhibitors. Some fibric acid analogues (but not gemfibrozil), however, are reported to increase the serum creatinine level. Combination therapy should be used with caution because it increases the risk for myositis and rhabdomyolysis.

TABLE 10.3 American Heart Association and American College of Cardiology Recommendations for the Primary Prevention of Coronary Heart Disease

Risk Intervention and Goals	Recommendations
Smoking cessation	• Query at each visit • Advise to quit • Help with counseling and pharmacotherapy • "Ask, advise, assess, assist, and arrange"
Blood pressure control	Lifestyle modification (restrict salt intake, moderate ethyl alcohol use, and physical activity)
Dietary intake	Modify food choices to reduce saturated fats and trans fats
Aspirin	Low-dose aspirin
Dyslipidemia	Treat appropriately; see below
Physical activity	At least 30 minutes of moderate—intensity physical activity on most days (and preferably all) days of the week

Weight management	Weight reduction of 10% in the first year of therapy
Diabetes	Maintain hemoglobin A_{1c} <7%

TABLE 10.4 American Heart Association and American College of Cardiology Recommendations for Secondary Prevention for Patients with Coronary Artery Disease

Goals	Intervention
Smoking: goal is complete cessation	Ask, advise, assess, and arrange
Blood pressure control: goal is to maintain blood pressure < 130/80 mm Hg	See Table 9.10
Lipid management: primary goal is LDL-C <100 mg/dL; secondary goal, if TG ≥200 mg/dL, HDL ≤40 mg/dL	See Table 9.9
Physical activity: minimum goal is 30 min, 3-4 d/wk; optimum is daily	Assess risk

Weight management: goal is BMI of 18.5 to 24.9 kg/m2	Calculate BMI and measure waist circumference Follow weight Waist circumference <88 cm (<35 inches) in women Waist circumference <102 cm (<40 inches) in men
Diabetes management: goal is HbA_{1c} <7%	Appropriate therapy to maintain HbA_{1c} <7%
Antiplatelet agents, anticoagulants	Indefinitely on aspirin (75-325 mg)
ACE-I	Indefinitely for all post-MI patients unless contraindicated
β Blockers	Indefinitely in all post-MI patients

ACE-I, angiotensin-converting enzyme inhibitor; BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglycerides.

STRATEGY 6: TREAT HYPERTENSION AGGRESSIVELY

Hypertension occurs in 60% to 80% of renal transplant recipients. It is associated with an increased risk for graft failure. Studies in the general population show that treatment with antihypertensive agents reduces the risk for CVD. There is good reason to believe that treating blood pressure elevations would be beneficial in renal transplant recipients.

All classes of antihypertensive agents can be used to lower blood pressure in renal transplant recipients. Although there are limited data on the effects of reduced dietary sodium chloride intake on blood pressure in renal transplant recipients, this is a reasonable first step. A low dose of thiazide diuretic is also reasonable for patients with creatinine clearance estimated to be greater than 25 to 30 mL per minute. Low doses of thiazides (e.g., 12.5 to 25 mg per day) are effective and do not generally perturb lipid or glucose metabolism. Both a lowsalt diet and thiazide diuretics may help with edema, which is a common problem after transplantation. A thiazide diuretic may also help in the management of the hyperkalemia that is common in CNI-treated transplant recipients. Transplant recipients may be sensitive to volume contraction; therefore, diuretics may cause a reversible increase in serum creatinine levels. Thiazides often potentiate the antihypertensive effects of other agents, especially ACEIs. Thiazides are inexpensive. β Blockers are also relatively inexpensive and are especially attractive for patients with ischemic heart disease, which is common after renal transplantation. Relative contraindications to β blockers (e.g., peripheral vascular disease, reactive airways disease, and hypoglycemic reactions) are rarely a reason to forego the use of this important class of medication.

Physicians are sometimes reluctant to use ACEIs and angiotensin II antagonists in transplant patients for fear of inducing hemodynamic impairment of allograft function. Several studies, however, show that these drugs are generally safe, effective, and well tolerated. They may reduce proteinuria and stabilize the deterioration in renal function in chronic allograft failure, possibly reducing the production of transforming growth factor-β (TGF-β). They may also have additional benefit in reducing the incidence of cardiovascular events in high-risk patients, and may also reduce the degree of insulin resistance. Occasionally, ACEIs may increase serum creatinine, but this is usually a transient and reversible effect. Hyperkalemia can often be managed by adding a thiazide diuretic or a loop diuretic to the treatment regimen. ACEIs may cause anemia in transplant recipients; this side effect can be exploited for the treatment of post-transplantation erythrocytosis. Cough occurs in about 15% of patients taking ACEIs but is much less frequent with ARBs. Otherwise, ARBs appear to have all of the advantages and disadvantages of ACEIs.

Calcium antagonists are also effective in renal transplant recipients. They can contribute to edema, which is already prevalent among transplant patients. Calcium

antagonists appear to improve the preglomerular, arterial vasoconstriction that mediates cyclosporine-induced declines in renal blood flow. They may help to alleviate the propensity of the CNIs to exacerbate delayed graft function immediately after deceased donor transplantation. Nondihydropyridine calcium antagonists (e.g., diltiazem and verapamil) increase calcineurin inhibitor blood levels and can be used to help reduce the immunosuppressive drug cost. Dihydropyridine calcium antagonists have less effect on blood levels (see Chapter 5, Part I). Calcium antagonists may cause gum overgrowth, particularly when used with cyclosporine. Vasodilators and α blockers are also effective in treating hypertension, although they can cause reflex tachycardia and may need to be used in combination with β blockers. Excess hair growth with minoxidil, the most potent vasodilator, limits its long-term usefulness in women. Other agents that are useful include sympatholytics, central and peripheral α antagonists, and combined α and β blockers. Readers are referred to the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of hypertension (see "Selected Readings"). Most patients require combination therapy. Some require several agents.

When hypertension cannot be controlled, particularly if attempts to reduce blood pressure result in decreased graft function, the possibility of renal

---

allograft artery stenosis should be considered (see Chapter 8). In addition, the presence of diuretic-resistant peripheral edema, a loud allograft bruit, renal dysfunction after administration of ACEIs or ARBs, and polycythemia should engender consideration of this diagnosis. Color-flow Doppler examination of the renal artery may aid the diagnosis, but interpretation of this test is difficult, and false-positive results are common. Radionuclide scanning is usually not helpful. Magnetic resonance angiography or renal arteriography should be used for diagnosis when suspicion of renal allograft artery stenosis is high, paying attention to the risk for iodine-containing dyes worsening renal function, and that of gadolinium causing nephrogenic fibrosing dermatitis in patients with a reduced GFR (see Chapter 13). The studies to exclude renal artery stenosis should also include studies of the proximal iliac artery because stenosis of this is not uncommon, and the effects may mimic those of renal artery stenosis. Percutaneous transluminal angioplasty may improve renal function and reduce the need for antihypertensive medications in 60% to 85% of cases. Restenosis may occur in up to 30%. Surgery should probably be reserved for critical stenosis that threatens the integrity of the graft.

The native kidneys often contribute to hypertension after renal transplantation. Studies to determine the role of the native kidneys in causing hypertension, however, are probably not useful. In particular, renal vein renins do not reliably predict blood pressure reduction after native kidney nephrectomy. Therefore, in difficult-to-control hypertension, consideration should be given to empirical removal of the native kidneys. Laparoscopic surgery may reduce the morbidity of post-transplantation native kidney nephrectomy.

STRATEGY 7: TREAT DIABETES MELLITUS AGGRESSIVELY

Diabetic patients are at continued elevated risk for developing CVD and other diabetic complications, including diabetic nephropathy. This is also true for those who develop new-onset diabetes after transplantation, who very rapidly develop comparable risks for CVD and death as patients already diabetic when transplanted. Abnormalities in glucose tolerance also occur in up to 30% of post-transplantation patients in the absence of a pretransplantation or post-transplantation diagnosis of diabetes; such abnormalities are less common in patients receiving cyclosporine compared with tacrolimus. The targets of treatment are the same as for all diabetic patients, and sufficiently intensive treatment should be given to maintain a hemoglobin A1C lower than 7.0, even if this means the permanent use of insulin. These patients benefit from referral to a dietitian and an endocrinologist and should have the usual regular surveillance for vascular, ophthalmic, and neurologic disease. Their feet should be examined at every visit, particularly if they have a neuropathy. Aggressive treatment has been shown to reduce the risk for developing diabetic complications, including CKD and CVD. They should be treated with an ACEI or ARB, especially have they have any microalbuminuria. The immunosuppressive regimen should be evaluated to ensure that an excessive steroid dose is not being administered and to consider switching calcineurin inhibitor (see Chapter 5).

STRATEGY 8: ENCOURAGE A HEALTHY LIFESTYLE

Regular aerobic exercise should be part of the therapeutic regimen of all patients at high CVD risk and may be particularly beneficial in counteracting the effects of corticosteroids on muscle and bone. Near-normal levels of physical functioning are possible after transplantation, particularly for those patients who engage in regular physical activity. Patients should be encouraged to train for and participate in the Transplant Games. Exercise may help to minimize post-transplantation weight gain and may be particularly important for patients

---

with the metabolic syndrome. Readers are referred to Chapter 19 for detailed dietary recommendations for transplant patients.

Cigarette smoking appears to be just as prevalent among renal transplant recipients as it is in the general population. Cigarette smoking contributes to CVD and increases the already high risk for cancer after renal transplantation. Studies in nontransplanted populations also show smoking to be detrimental to renal function. Thus, every effort should be made to encourage transplant recipients to quit smoking. Smoking cessation programs that make use of nicotine-replacement therapies have been shown, in clinical trials, to be effective. The American and Psychiatric Society and the Agency for Health Care Policy and Research have developed guidelines for smoking cessation.

Aspirin prevents CVD events for patients with known CVD. The role of aspirin

prophylaxis in primary prevention is clear. Aspirin should be considered for renal transplant recipients with CVD, and possibly for patients who are at high risk for CVD events.

STRATEGY 9: SCREEN FOR CANCER

After transplantation, there is a substantially increased incidence of a wide variety of cancers, most of which have known or suspected viral etiology. Readers are referred to the large database of the Australia and New Zealand Transplant Registry for the relative incidence of common malignancies in dialysis and transplant patients (see Vajdic and colleagues in “Selected Readings”). Knowledge that many post-transplantation cancers are caused by viruses has not yet produced effective prophylactic strategies. Successful treatment of cancer after renal transplantation relies on surveillance and early detection. Typically, guidelines for cancer screening developed for the general population are presumed to be relevant to renal transplant recipients. However, because the life expectancy of most transplant patients is less than that of the general population, the presumptions underlying recommendations for cancer screening may not be relevant to them. Decisions regarding routine screening for breast, prostate, lung, and colorectal cancers should be made on an individual basis because their incidence does not differ greatly in the transplant population from the general population. Cervical carcinoma is more prevalent in transplant recipients, and women who are older than 18 years should have an annual pelvic examination and Papanicolaou test. Anogenital carcinoma is common after renal transplantation. Yearly physical examination and pelvic examination in women are useful for screening for anogenital lesions.

Skin cancers are common after renal transplantation. Annual self-examination and examination by a physician are warranted to screen for squamous cell carcinoma and malignant melanoma. Suspicious lesions should undergo biopsy. Patients should be instructed to avoid sun exposure and to use sunblock, although the effectiveness of this strategy in adults is uncertain. Patients with multiple lesions should undergo formal dermatologic surveillance on a regular basis. In addition to local measures, oral isotretinoin may be beneficial and appears to be safe in transplant recipients.

The management of immunosuppression in patients who have developed cancer is difficult, and each case should be considered individually. There is clinical evidence that higher cyclosporine levels are associated with an increased incidence of cancer and experimental evidence that cyclosporine may accelerate the growth of metastatic cancer. It is unlikely that this finding is specific for cyclosporine; therefore, it is wise to minimize the immunosuppressive protocol, and in some cases, discontinuation of immunosuppression may be appropriate. The potential for graft loss needs to be weighed against the natural history and the staging of the malignancy. It is the patient who must

ultimately decide on his or her priorities after receiving consultation from oncologic and transplant physicians.

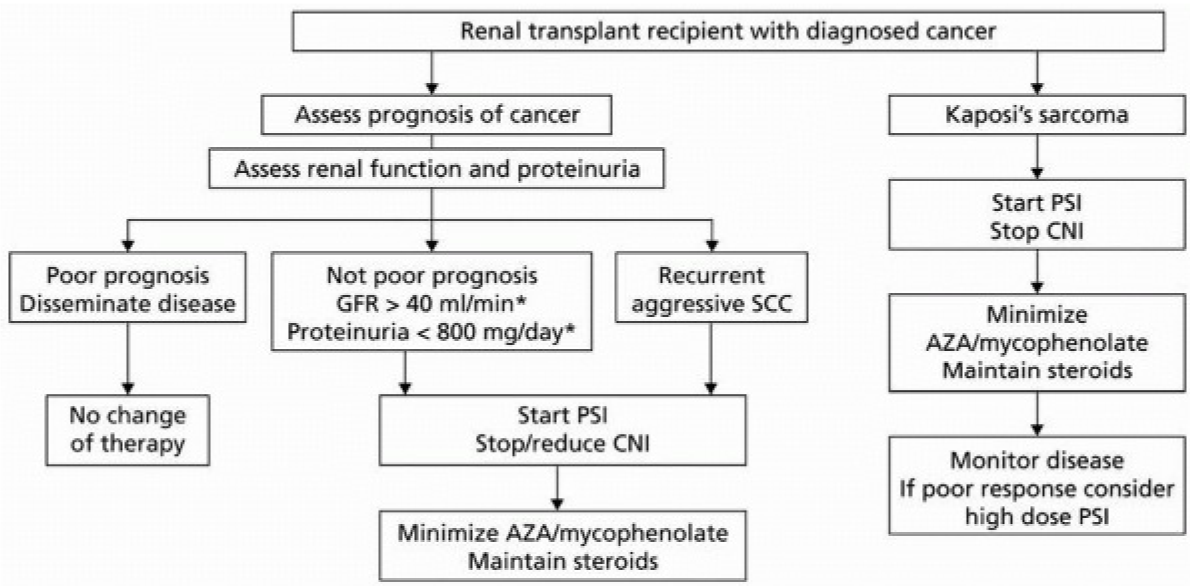


FIGURE 10.2 Recommendations to guide conversion from calcineurin inhibitors to proliferation signal inhibitors in renal transplant recipients. AZA, azathioprine; CNI, calcineurin inhibitor; PSI, proliferation signal inhibitor; SCC, squamous cell carcinoma. *Some clinicians may decide to convert patients with impaired renal function (e.g., GFR <40 mL/min, proteinuria >800 mg/day) if they feel that the benefits of PSIs are warranted; this should be evaluated on an individual patient basis. (From Campistol J, Albanell J, Arns W. Use of proliferation signal inhibitors in the management of post-transplant malignancies: clinical guidance. Nephrol Dial Transplant 2007;22[Suppl 1]:36-41, with permission.)

There is a growing body of clinical data that suggests that TOR inhibitors (sirolimus and everolimus) are associated with a reduced risk for malignancy after transplantation (see Chapter 5, Part I). There are also theoretical reasons for basing immunosuppression on these drugs in patients with *de novo* post-transplantation malignancies. The benefit of this approach, however, has not been definitively established, but a useful algorithm to guide conversion from calcineurin inhibitors to TOR inhibitors has been proposed and is shown in Figure 10.2 (in this figure, the term *proliferation signal inhibitor*, or *PSI*, is used rather than the term *TOR inhibitor*). Post-transplantation lymphoproliferative disease (PTLD) is discussed later.

STRATEGY 10: PREVENT INFECTION

Infections in the late post-transplantation period are discussed in Chapter 11 together with recommendations for routine immunization (Table 11.4). Routine prophylaxis for

Pneumocystis carinii infections with trimethoprim-sulfamethoxazole is probably not warranted late after transplantation. The exception may be for patients who are receiving high doses of immunosuppression to treat rejection or for patients receiving sirolimus (see Chapter 5, Part I). The same is true for cytomegalovirus (CMV) infection prophylaxis. Although recurrent urinary tract infections are common, there is no evidence that routine prophylactic antibiotic therapy is effective.

Influenza types A and B are likely to be at least as common, and probably more severe, in renal transplant patients as in the general population. Therefore, transplant recipients should receive annual influenza vaccination. Although vaccines are safe, they may be somewhat less effective in transplant recipients than in the general population because of the limitation in antibody

---

response by immunosuppressant drugs. Nevertheless, the response to vaccination is high enough (50% to 100%) to warrant their use.

STRATEGY 11. PROTECT THE BONES

Immunotherapy and secondary hyperparathyroidism are the most important pathogenic factors leading to bone disease and fractures after transplantation. In addition to the well-documented osteopenic affect of steroids, cyclosporine has been associated with bone mineral density (BMD) loss (though there is no difference in post-transplantation BMD between patients who receive cyclosporine or tacrolimus). Other implicated factors include preexisting uremic osteodystrophy, β_2-microglobulin-associated amyloidosis, and diabetic osteopathy. Cross-sectional studies consistently show that bone mass is lower in transplant recipients than in age- and sex-matched controls. Vertebral bone loss is the highest in the first 6 to 12 months after transplantation (3% to 9%) but tends to stabilize thereafter. A fracture rate of about 3% has been described in nondiabetic kidney transplant recipients, and this figure may be considerably higher in diabetic recipients of kidney and pancreas transplants. There is a clinical impression that the post-transplantation fracture rate is decreasing, likely as a result of reduced steroid dosage and better control of bone disease before transplantation.

It is reasonable to screen for decreased BMD at baseline and 6 months after transplantation with dual-energy x-ray absorptiometry (DEXA) of the lumbar spine and hip. Patients with decreased BMD may be candidates for oral calcium and vitamin D supplementation (see Chapter 19), bisphosphonates, and occasionally calcitonin. Patients with abnormal bone mineral density 6 months after transplantation should be considered for additional follow-up examinations to measure the effectiveness of therapy. Bisphosphonates, which inhibit osteoclast activity, are effective in treating post-transplantation osteopenia. Both bisphosphonates and calcitriol reverse bone loss and increase bone mass, although the resultant impact on the fracture rate is unproved. Bisphosphonates are more effective than calcium supplementation and vitamin D metabolites, although they may be contraindicated in the occasional patient

with bone disease characterized by low turnover diagnosed on bone biopsy. Alendronate is licensed by the U.S. Food and Drug Administration (FDA) for steroid-induced osteoporosis. It is difficult to prove a direct relationship between corticosteroid dose and bone loss, but it is reasonable to minimize steroid dose or consider discontinuation in patients at high risk. Most of the impact of corticosteroids on bone comes from the high doses given in the early post-transplantation period or for the treatment of acute rejection. Very low maintenance doses appear to have little effect on bone.

Corticosteroids can also cause avascular necrosis (AVN) or osteonecrosis. The site for post-transplantation AVN is the femoral head in nearly 90% of cases. The incidence of AVN is difficult to assess but has been reported to be close to 1% per year in the second and third post-transplantation years, and an overall incidence of 5.5% has been reported. These data are likely representative of a time when steroids were used more liberally than is current practice. The pathogenesis of AVN is poorly understood, and although corticosteroids can be implicated in most cases, it has proved difficult to establish a meaningful doseresponse effect. AVN usually presents as hip or groin pain exacerbated by weight bearing. Pain may also be referred to the knee. Magnetic resonance imaging is the most sensitive method for diagnosis. Core decompression before the femoral head collapses may relieve pain, but about 60% of cases require total hip arthroplasty. Fortunately, the need for these procedures has been reduced considerably.

Hypophosphatemia is common early after transplantation (see Chapter 9) but is less common in the late post-transplantation period. When hypophosphatemia

---

is encountered in the late post-transplantation period, it is often caused by the tertiary hyperparathyroidism of CKD that remains unresolved: parathyroid hormone (PTH) levels should be measured. Hypophosphatemia has also been described with normal PTH levels and has been ascribed to a novel growth factor, phosphotonin, whose levels accumulate in CKD. On the other hand, hyperphosphatemia may also be encountered, usually in transplant recipients with renal insufficiency. Dietary management is discussed in Chapter 19.

Persistent hyperparathyroidism is observed in about 50% of patients 1 year after transplantation. If increased PTH levels cannot be suppressed, particularly if hypercalcemia becomes problematic, cinacalcet can be given at a starting dose of 30 mg daily. Careful monitoring of calcium and phosphorus levels is initially required. Cinacalcet, however, is only approved in the United States for the treatment of hyperparathyroidism in dialysis patients, although reports suggest that it can be used effectively and safely after transplantation. Parathyroidectomy may be required if calcium and PTH levels remain elevated.

Hypomagnesemia is seen in about 10% of renal transplant recipients treated with CNIs. Hypomagnesemia may play a role in post-transplantation hyperlipidemia and

hypertension. Treatment is usually by oral magnesium replacement.

STRATEGY 12: REGARD PERSISTENTLY IMPAIRED POST-TRANSPLANTATION FUNCTION AS A FORM OF CHRONIC KIDNEY DISEASE

Even well-functioning kidney transplants may have a GFR that falls within the definition of CKD (see Chapter 1, Table 1.1). CAF is a form of CKD that progresses to end-stage renal disease (ESRD) and the need for dialysis and transplantation. Patients should understand that “leading a normal life,” the aim of transplantation, includes following quite precise recommendations for health maintenance. A balance needs to be struck by patients and their doctors between burdensome instructions and living the good life. It is clear, however, that patients with impaired baseline renal function are not normal, and their care should encompass the same principles that have become standard of care for other causes of CKD. Control of hypertension, use of ACEIs, control of mineral metabolism, treatment of anemia, and eventually preparation for ESRD options and timely dialysis access placement are fundamental to optimal long-term post-transplantation care. The immunosuppressive management of the failing graft is discussed in Chapter 5, Part V.

SPECIFIC MANAGEMENT ISSUES

Post-transplantation Lymphoproliferative Disease

The reported incidence of PTLD in the recipients of solid-organ transplants ranges from 0.8% to 15% and varies with the type of transplantation, the patient's age, and the immunosuppressive regimen employed. The incidence is about 12-fold higher than in the nontransplant population. Most cases are recognized within the first post-transplantation year. For kidney transplant recipients, the incidence is typically 1% to 2%. Despite the widespread use of potent immunosuppressive protocols, the incidence of PTLD in kidney transplant recipients does not appear to be increasing.

PTLDs have several unusual features that distinguish them from lymphomas found in the general population:

1. Most are non-Hodgkin lymphomas (Hodgkin disease is the most common lymphoma in age-matched controls), are of B-cell origin, and are $CD20^{+}$.

---

2. PTLD often presents as dysfunction of the transplanted organ and may be confused histologically with severe rejection. Disease is often localized in or near the allograft.

3. There is a high rate of association with Epstein-Barr virus (EBV) infection. Seronegative recipients of an organ from a seropositive donor are at highest risk for PTLD.

4. Extranodal involvement (central nervous system, liver, lungs, kidneys, intestines) is common, and multiple sites are often involved.

5. The mortality rate is much greater with PTLD than with lymphomas in the general population. The course may be extremely fulminant, with progression to death within a few months of transplantation.

6. The prolonged or repeated administration of lymphocytic-depleting antibody preparations is a significant risk factor for the development of PTLD.

7. PTLD may respond to withdrawal or drastic reduction of immunosuppressive therapy. Standard chemotherapy and irradiation are not generally helpful and may exaggerate the degree of immune compromise.

8. Viral infection, particularly with CMV infection (see Chapter 11), may serendipitously reduce EBV replication and the incidence of PTLD.

9. Although typically considered to result from EBV infection of recipient B cells, PTLD may be of donor origin in some patients.

Role of Epstein-Barr Virus

EBV is a human DNA-transforming herpesvirus that primarily targets B lymphocytes. It is associated with an array of disorders ranging from infectious mononucleosis to nasopharyngeal carcinoma, Burkitt lymphoma, and B-cell lymphomas in immunocompromised patients.

Transmission of EBV in transplant recipients is most commonly through the transplanted organ. EBV undergoes lytic replication because of inadequate EBV immune surveillance. The resultant increased burden of EBV in the naive recipient then infects the recipient's B cells. EBV has the innate capability of transforming and immortalizing host B lymphocytes, producing *lymphoblastoid cells*. An extrachromosomal particle of EBV genome can be found within the B-cell nucleus. In an immunocompetent host, a latent carrier state is established when the proliferation of the transformed B cells is contained by a normal immune response with intact cell-mediated immunity. About 95% of adults have serologic evidence of previous EBV infection. The presence of reactive T lymphocytes inhibits infected cell proliferation in a process called *regression*. Immunosuppressive agents, particularly the antilymphocytic antibody preparations (see Chapter 5), prevent regression, and EBV-transformed cells may proliferate uncontrollably. The number of EBV DNA copies has a high positive predictive value for the diagnosis of PTLD; however, renal transplant patients can have a fluctuating serologic load without development of PTLD, and there is a poor correlation between the serologic evidence of EBV reactivation and EBV viral load.

EBV-associated PTLD appears to progress through stages of transformation to a malignant state. The first stage resembles an infectious mononucleosis syndrome, with the development of polymorphic diffuse B-cell hyperplasias without cytogenic

abnormalities or gene rearrangements. The second stage produces a subpopulation of cells with cellular and nuclear atypia and cytogenic abnormalities. In the third stage, a malignant monoclonal B-cell lymphoma develops. A form of fulminant PTLD has been described, often following multiple courses of lymphocytic depletional agents. The disease may initially resemble a severe infectious mononucleosis-like illness but may progress rapidly,

with death occurring within a few months of transplantation. At a later stage, the patient may present with localized lymphoproliferative tumor masses in the brain, lung, or gastrointestinal tract. Predictors of poor survival from PTLD include increased age, elevated lactic acid dehydrogenase values, severe organ dysfunction, multiorgan involvement, and constitutional symptoms (fever, night sweats, weight loss).

Clonality

The issue of clonality of post-transplantation lymphomas has been a source of dispute. It has been suggested that polyclonal B-cell lesions are likely to be benign and to respond to withdrawal of immunosuppression and acyclovir, whereas monoclonal lesions are believed to be frankly malignant. In fact, polyclonal lymphoproliferative disorders may represent an early stage in a spectrum that progresses from polyclonal activation of B cells by EBV to latently infected, malignantly transformed, monoclonal B-cell lymphomas.

Treatment

Restoration of host immunity is probably the most important therapy for the control of lymphoid proliferation. Patients with evidence of polyclonality are most likely to respond to reduction of immunosuppression. For patients with monoclonal tumors, immunosuppression should be drastically reduced or discontinued altogether.

Results with conventional cytoxic therapy and radiotherapy have been disappointing, with mortality rates remaining at greater than 80%. Several small series of PTLD have been reported in which treatment with the anti-CD20 monoclonal antibody rituximab has been successful. B cells, together with their EBV viral load, disappear from the blood after its administration. The success rate of rituximab is estimated to be 65%. Rituximab and rapamycin combinations have also been reported to be effective and a novel treatment has been reported using an infusion of EBV-specific cytotoxic T-cells. Most patients in whom immunosuppression is stopped lose their grafts to inexorable rejection. Occasionally, tumors regress and the patients and their grafts can be maintained on very low dose immunosuppression. It is recommended that these patients should not be retransplanted for at least 2 years, even if there is no sign of residual disease.

Hematologic Disorders

Anemia

Anemia is common after renal transplantation. The presumption that the newly transplanted kidney will produce enough erythropoietin to lead to resolution of pretransplantation and early post-transplantation anemia is incompletely realized in many patients. It has been estimated that 25% of patients are anemic and 13% are iron deficient 12 months after transplantation. In addition to its clinical symptoms, anemia has been associated with worse patient and graft survival and higher rates of acute rejection compared with nonanemic transplant recipients, and it may further exaggerate left ventricular hypertrophy. Unrecognized iron deficiency is a frequent cause, and gastrointestinal bleeding should be excluded. Anemia from folate or vitamin B_{12} deficiency is unusual. Hemolysis is rare. In the late post-transplantation period, anemia is most commonly caused by immunosuppression or decreased renal function. Azathioprine, mycophenolic acid, and sirolimus can cause anemia, thrombocytopenia, and leukopenia, and the doses of these medications may need to be reduced. Anemia has been reported in as many as 60% of patients receiving sirolimus. ACEIs and ARBs may also cause anemia. Parvovirus infection may be a cause of refractory anemia, and treatment with intravenous immune globulin might be effective. When no underlying cause can be found, renal function is impaired, and iron stores are adequate, erythropoietin or darbepoetin alfa (Aranesp) may be indicated. Observing changes in the reticulocyte count that precede an increase in the hemoglobin level can monitor the efficacy of therapy. Anemia in patients with chronic allograft failure should be treated no less aggressively than the anemia accompanying other causes of chronic renal failure. The guidelines for the use of erythropoietin have come under scrutiny because of concerns relating to an increase in CVD if the targeted hemoglobin is too high and because of possible effects on cancer growth. Current recommendations for the use of this drug in CKD should be used in treating transplant patients.

Erythrocytosis

Erythrocytosis is encountered in up to 20% of patients after transplantation, most commonly during the first 2 years. It rarely occurs in patients who have undergone native kidney nephrectomy, suggesting that it is the native kidneys, rather than the transplant, that is the source of the problem, although stenosis of the transplant renal artery may be a factor. The cause of erythrocytosis appears to be related to defective feedback regulation of erythropoietin metabolism. Although increased erythropoietin production has been reported after transplantation, erythrocytosis is not directly related to erythropoietin levels, which may be low or undetectable in some cases. Elevated levels of insulin-like growth factor-1 (IGF-1) have been found, which may increase the sensitivity of erythroid precursors to erythropoietin. Erythrocytosis may also be a manifestation of transplant renal artery stenosis, and this diagnosis should be considered in any patient with the combination of hypertension, edema, allograft bruit,

and erythrocytosis.

Hematocrit levels higher than 60% are associated with increased viscosity and thrombosis, and treatment should commence at a hematocrit level of greater than 55%. Low doses of ACEIs and ARBs are generally effective in reducing elevated hematocrit levels. Their mechanism of action may be related to the induction of apoptosis in erythroid precursors and to reduction of IGF-1 levels. Renal dysfunction after introduction of ACEIs should raise the possibility of transplant renal artery stenosis. Theophylline is a potential alternative to the use of ACEIs or ARBs, although it is less-well tolerated. Phlebotomy may be required in resistant cases.

POST-TRANSPLANTATION REPRODUCTIVE FUNCTIONS

Men

After successful transplantation, about two thirds of male patients observe improved libido and a return of sexual function to predialysis levels. In some patients, there is no improvement, and occasionally sexual function deteriorates. Fertility, as assessed by sperm counts, improves in half of patients. The sex hormone profile tends to normalize; plasma testosterone and follicle-stimulating hormone levels increase; and luteinizing hormone levels, which may be high in dialysis patients, decrease to normal or low levels. Cyclosporine may impair testosterone biosynthesis through direct damage to Leydig cells and germinal cells, and a direct impairment of the hypothalamic-pituitary-gonadal axis has been suggested. Sirolimus may also reduce testosterone levels. There is no increased incidence of neonatal malformations in pregnancies fathered by transplant recipients.

Additional factors may account for failure of male sexual function to improve after transplantation. Antihypertensive medications may be responsible in some patients, autonomic neuropathy may impair erectile function, and

---

interruption of both hypogastric arteries may occasionally impair vascular supply. Male patients should be asked about their sexual function and referred for urologic evaluation when necessary. There is no specific contraindication to the use of sildenafil (Viagra) or similar agents in transplant recipients as long as standard precautions are taken regarding concomitant coronary artery disease (CAD).

Women

Women with CKD demonstrate loss of libido, anovulatory vaginal bleeding or amenorrhea, and high prolactin levels. Maintenance dialysis therapy results in improvement in sexual function in only a small percentage of women, and pregnancy is rare. After successful transplantation, fertility may be restored rapidly, menstrual function and ovulation typically return, and prolactin levels fall to normal in most women by the end of the first year.

Family Planning

All women of childbearing age should be counseled concerning both the possibility and the associated risks of pregnancy after kidney transplantation. Psychosocial issues should be discussed, genetic counseling should be provided for those with hereditary kidney disease, and consideration should be given to the long-term prognosis of the patient and the graft. Patients can be assured that birth defects are not increased with the use of azathioprine, cyclosporine, and tacrolimus during pregnancy, although some degree of intrauterine growth retardation and prematurity are common. Data regarding the stability of graft function during and after pregnancy should be discussed. All pregnancies should be planned and prepared for. Conception should be delayed 18 to 24 months after kidney transplantation and contraception practiced until then.

Contraceptive counseling should begin immediately after transplantation because ovulatory cycles may begin within 1 to 2 months of transplantation in women with well-functioning grafts. Low-dose estrogen-progesterone oral contraceptive preparations are advised. They should be used with caution because they may cause or aggravate hypertension or precipitate thromboembolism. CNI levels should also be monitored soon after the contraceptive is started. The long-acting, subcutaneously placed hormone preparations are highly effective and well tolerated. They have not yet been formally evaluated in the transplantation situation and should be used only under careful supervision. The risk for infection may be increased with the use of an intrauterine device in immunocompromised patients, and their efficacy may be compromised by the antiinflammatory properties of the immunosuppressive agents. Barrier contraception is the safest modality but depends on user compliance for efficacy.

PREGNANCY

Women with ESRD sometimes seek transplantation with the knowledge that a well-functioning graft will give them the only real chance for natural motherhood. It has been estimated that 2% of women of childbearing age conceive after transplantation. The incidence of spontaneous abortion is reported to be 13%, and that of ectopic pregnancy is reported to be 0.5%. These frequencies are not different from those seen in the normal population. About one third of pregnant transplant recipients seek therapeutic abortion, a number that likely reflects inadequate family planning in women who have not previously considered themselves to be fertile. More than 90% of conceptions that continue beyond the first trimester end successfully.

Table 10.5 lists the criteria that should ideally be met before conception. A 90% incidence of successful pregnancies has been reported for women with a

---

baseline serum creatinine of 1.5 mg/dL or less. A higher serum creatinine level increase the risk for post-transplantation graft loss, which consistently occurs within 2 years of pregnancy in women whose baseline creatinine is greater than 2 mg/dL. Failure to

meet all the listed criteria places the patient in a higher risk category but is not necessarily an absolute contraindication to pregnancy. The U.S. National Transplantation Pregnancy Registry has been developed to provide current information concerning transplant recipient pregnancy for the benefit of patients and their physicians.

TABLE 10.5 Criteria for the Reduction of Post-transplantation Pregnancy Risk

At least 1 year after transplantation
Serum creatinine < 2.0 mg/dL, preferably < 1.5 mg/dL
No recent episodes of acute rejection
Normotensive or minimal antihypertensive regimen
Minimal or no proteinuria
Normal allograft ultrasound
Pregnancy-safe drug regimen (see text)

Antenatal Care

Pregnancy in a patient with a kidney transplant should be considered a high-risk condition and should be monitored in a tertiary care center with consultation by a transplantation nephrologist, obstetrician, and pediatrician. The pregnancy should be diagnosed as early as possible, and accurate dating obtained by fetal ultrasound. For patients with good allograft function before conception, the GFR remains stable or increases, as it does during a normal pregnancy. The GFR may decline to pregnancy values during the third trimester. Most studies suggest that pregnancy does not have an unfavorable effect on long-term graft function as long as baseline function is excellent. Proteinuria may increase to abnormal pregnancy in the third trimester but usually resolves postpartum and is of no prognostic significance unless it is associated with hypertension. About 30% of pregnant patients with kidney transplants develop pregnancy-induced hypertension, a figure that is fourfold greater than in uncomplicated pregnancies. The use of cyclosporine in pregnancy tends to increase the incidence of hypertension. If complications (usually hypertension, renal deterioration, and rejection) occur before 28 weeks' gestation, successful obstetric outcome is reduced by 20%. Prematurity (60%), growth restriction (52%), and the need for hospitalization in a neonatal intensive care unit (35%) are reported to be more common in transplant recipients than in patients with renal diseases who are not on immunosuppression.

Urinary tract infections are the most common bacterial infections and occur in up to 40% of pregnant transplant recipients. Pyelonephritis may develop despite adequate antibiotic treatment. Urinary tract infections are particularly common in patients who develop ESRD as a consequence of pyelonephritis.

Immunosuppression in Pregnancy

Prednisone

Prednisone crosses the placenta, but a large proportion is converted to prednisolone, which allegedly does not suppress fetal corticotropin. Adrenal insufficiency in the neonate has been reported with maternal prednisone ingestion. Very large doses of corticosteroids administered to animals have resulted in

---

congenital anomalies (cleft lip and palate), but no consistent abnormalities have been noted in the offspring of women treated with corticosteroids during pregnancy for rheumatologic disease or kidney transplantation. Overall, prednisone is considered to be relatively safe for use in pregnancy.

Azathioprine

At doses of 2 mg/kg or less, no anomalies attributable to azathioprine have been noted in human offspring. There are minimal data, however, on the long-term effects of azathioprine on first- or second-generation offspring. Azathioprine can cause transient gaps or breaks in lymphocyte chromosomes. Germ cells and other tissues have not been

studied. It is not known whether the eventual sequelae could be the development of malignancies in affected offspring or other abnormalities in the next generation.

Calcineurin Inhibitors

There are no animal or human data showing teratogenicity or mutagenicity of cyclosporine or tacrolimus, which appear to be safe during pregnancy. Intrauterine growth retardation and small-for-gestational-age neonates have been reported with cyclosporine use and may reflect chronic vasoconstriction. Cyclosporine is present in the fetal circulation at the same concentration found in the mother. The increased volume of distribution may produce low maternal blood levels, and dose elevations may be required.

Mycophenolic Acid

The FDA has added a “black box” warning to the product insert for mycophenolic acid preparations following a number of reports of congenital fetal abnormalities in children borne to women taking these drugs at the time of and after conception. These include abnormalities of the face and ear. Women should be advised to discontinue these drugs for some months before attempting conception.

Other Immunosuppression

The FDA categorizes the potential fetal risks of drugs used in pregnancy. Most immunosuppressive drugs fall into category C, which implies that “risks cannot be ruled out.” Limited data are available concerning the safety of pregnancy for patients receiving newer immunosuppressive agents (see Chapter 5); for the present, they should be avoided during pregnancy. Sirolimus should be discontinued 6 weeks before conception is attempted. At present, there is insufficient information about the biologic effect of even small amounts of immunosuppressive agents on the neonate, and breast-feeding should be discouraged.

Hypertension Control

Many transplant patients require antihypertensive drugs in pregnancy. Drugs that have been consistently shown to be safe should be used; these include methyldopa, hydralazine, and labetalol. ACEIs and ARBs are generally contraindicated in pregnancy, but it is probably safe to continue a pregnancy if their administration is discontinued as soon as pregnancy is diagnosed.

Labor and Delivery

Vaginal delivery is recommended because the transplanted kidney is placed in the false pelvis, and there is little risk for obstruction of the birth canal or mechanical injury to the allograft. Cesarean section is usually performed only for standard obstetric reasons.

Great care should be taken to identify and protect the transplanted ureter. Preterm delivery occurs in about half of pregnancies in

transplant recipients because of the frequent occurrence of declining kidney function, pregnancy-induced hypertension, fetal distress, premature rupture of membranes, and premature labor. The incidence of small-for-gestational-age neonates is 20%. There is no increase in fetal abnormalities.

In the perinatal period, the steroid dose should be augmented to cover the stress of labor and to prevent postpartum rejection. Hydrocortisone, 100 mg every 6 hours, should be given during labor and delivery. Maternal hypertension and fluid balance should be monitored carefully. Graft function and the immunosuppressive regimen should be monitored with particular care in the first 3 months postpartum. Occasional cases of postpartum acute renal failure resembling hemolytic uremic syndrome have been described.

PART II. CAUSES OF LATE ALLOGRAFT FAILURE DEFINING THE CAUSE OF ALLOGRAFT FAILURE

It is more difficult to define the cause of allograft failure than it may seem. Allograft failure is usually defined either by the patient's death or the patient's need to undertake new treatment for ESRD (i.e., chronic dialysis or retransplantation). Making a distinction between these two categories of allograft failure may have important implications for understanding how to prevent allograft failure. However, making the distinction may sometimes be difficult. For example, a patient with severe acute rejection may require dialysis support and may die of complications of immunosuppression before the rejection can be reversed. Did this patient die with a functioning graft, or was the graft loss because of acute rejection? Studies show, however, that most patients who die with a functioning graft have good allograft function (so-called death with graft function). In these cases, attempts to understand the pathogenesis of allograft failure should focus on understanding the cause of death and its pathogenesis. In the United States, death with graft function accounts for 40% to 50% of all graft losses (Figure 10.1).

The goal of renal transplantation should be to have every patient who dies do so with a kidney that functions well. Unfortunately, most deaths that now occur with a functioning allograft are premature and are potentially preventable. Most of the premature deaths that occur in the late post-transplantation period can be directly or indirectly attributed to the events that initially led to CKD and the consequences thereof (see Chapter 1) and to allograft dysfunction or the immunosuppression used to prevent or treat allograft rejection. The three most commonly defined causes of death in the late post-transplant period are CVD, infection, and malignancy.

CAUSES OF DEATH AFTER TRANSPLANTATION

Cardiovascular Disease

Atherosclerotic CVD kills patients by causing myocardial infarction, congestive heart failure, stroke, ischemic colitis, and peripheral vascular disease. In the case of ischemic colitis and peripheral vascular disease, the terminal event may be infection (e.g., sepsis from a perforated cecum or cellulitis). To understand how to prevent post-transplantation CVD deaths and complications, it is crucial to define the etiologic risk factors (Table 10.6). Identifying risk factors is important for two reasons. Some risk factors can be modified, and for some of these, there is strong evidence from studies in the general population that intervention improves survival. It is also important, however, to identify risk factors that cannot be modified because these risk factors help to identify high-risk patients who can be targeted for screening and possibly intervention as well as for treatment of other modifiable risk factors.

TABLE 10.6 Risk Factors for Post-transplantation Cardiovascular Disease

Risk Factor	Strength of Evidence
Pretransplantation cardiovascular disease	++++
Diabetes (including post-transplantation diabetes)	++++
Cigarette smoking	+++
Hyperlipidemia	+++
Hypertension	++

Platelet and coagulation abnormalities	++
Allograft dysfunction or rejection	++
Hypoalbuminemia	++
Erythrocytosis	+
Oxygen free radicals	+
Infections	+
Increased homocysteine	+

Patients with pretransplantation CVD are at increased risk for post-transplantation CVD complications. Such patients should be targeted for aggressive management of modifiable CVD risk factors. Because atherosclerosis is a systemic illness, it should not be surprising that patients with a history of cerebral vascular disease (e.g., ischemic strokes) are at increased risk for ischemic heart disease. Although pretransplantation CVD greatly increases the risk for post-transplantation CVD complications, much of the risk for CVD in the late post-transplantation period is acquired after transplantation. Identifying and aggressively managing high-risk patients is important. A decline in renal function has been identified as an important risk factor for CVD, and to the extent that the transplanted kidney is functioning well, this reduces the risk for CVD in transplant recipients. As renal function declines, this again becomes an additive risk factor for CVD.

Diabetes is the most common cause of ESRD leading to transplantation, and diabetes is the most important risk factor for post-transplantation CVD. Both type 1 and type 2 diabetes greatly increase the risk for ischemic heart disease, cerebral vascular disease, peripheral vascular disease, and death. Diabetic control may become difficult after transplantation and patients with type 2 diabetes often become insulin dependent.

About 20% of nondiabetic patients develop hyperglycemia after transplantation, and 5% to 10% require therapy with oral hypoglycemic agents or insulin. Older patients, obese patients, blacks, and patients with a strong family history of diabetes are at higher risk for post-transplantation diabetes. The effect of diabetes developed after transplantation on morbidity and graft survival is similar to that of pretransplantation diabetes. Corticosteroids and the calcineurin inhibitors (tacrolimus more so than cyclosporine) all contribute in varying degrees to glucose intolerance (see Chapter 5).

Numerous epidemiologic studies of the general population show that cigarette smoking is an important modifiable risk factor for CVD. Studies report that smoking is as prevalent in renal transplant recipients as it is in the general population. These same studies show that cigarette smoking is linked to CVD in the late post-transplantation period.

Countless epidemiologic studies and numerous large, randomized, controlled trials in the general population show that hyperlipidemia causes CVD.

The evidence is strongest that elevations in LDL cholesterol contribute to the pathogenesis of atherosclerosis; however, evidence is also strong that low levels of high-density lipoprotein (HDL) cholesterol also contribute to CVD risk. The evidence that hypertriglyceridemia is an independent risk factor for CVD in the general population is less convincing, and the main reason to treat hypertriglyceridemia is to reduce the risk for pancreatitis. Several studies have found the same associations between lipoprotein elevations and CVD in renal transplant patients. The most important cause of hyperlipidemia after renal transplantation is immunosuppressive medication. Sirolimus, cyclosporine, and tacrolimus (in order of severity) all cause elevations in lipid levels to varying degrees (see Chapter 5). Other causes include corticosteroid dose, diet, genetic predisposition, proteinuria, and possibly decreased renal function.

Data from several epidemiologic and interventional studies show that hypertension contributes to CVD in the general population, although it has proved difficult to demonstrate that hypertension specifically causes CVD in renal transplant recipients. This may be because most transplant physicians treat blood pressure aggressively. Corticosteroids and the CNIs (cyclosporine more so than tacrolimus) can elevate blood pressure after renal transplantation. Graft dysfunction also contributes to hypertension. Several studies also found that the presence of the native kidneys is associated with increased blood pressure after renal transplantation.

Observational studies found that allograft dysfunction is also associated with

subsequent CVD complications. Decreased renal function and proteinuria can contribute to other risk factors, such as hyperlipidemia, hypertension, and hyperhomocysteinemia. Allograft dysfunction is also more common in patients who have had acute rejection and have been treated with higher doses of immunosuppressive medications known to affect several CVD risk factors adversely. In some studies, however, allograft dysfunction was an independent risk factor for CVD. It is speculated that allograft rejection may be associated with a systemic inflammatory response that may contribute to the pathogenesis of CVD. Hypoalbuminemia may also be an independent risk factor for post-transplantation CVD, and chronic inflammation may reduce serum albumin levels. Atherosclerosis could be both a cause and an effect of chronic inflammation.

Although epidemiologic studies have often reported an association between antioxidant vitamin use and CVD, more convincing clinical data supporting a role for oxygen free radicals in the pathogenesis of CVD have been elusive. In particular, most large, randomized, controlled trials in the general population have failed to show that antioxidant vitamins protect against CVD events. Some evidence suggests that oxygen free radicals may be more prevalent and that antioxidant defenses may be more compromised in renal transplant recipients than in the general population.

A number of epidemiologic studies implicate various infections, including CMV infection, in the pathogenesis of CVD. In addition, some studies have found evidence for the presence of infectious agents in atherosclerotic lesions. It is certainly plausible, however, that individuals with CVD may be more susceptible to infection and that infectious agents may play an innocent-bystander role in systemic atherosclerosis. Heart transplant recipients treated with CMV prophylaxis have been reported to have less CAD. On the other hand, an association between CMV or other infections and CVD in renal transplant recipients has been difficult to document despite the fact that the prevalence of such infections is high. Periodontal disease is common in patients with CKD and may cause a systemic inflammatory response that may contribute to cardiovascular risk. Post-transplantation patients should maintain dental hygiene and have access to dental care.

Infection

Specific post-transplantation infections are discussed in Chapter 11. Infection is an inevitable companion of immunosuppression and is attributable to the overall level of immunosuppression. Certain infections occur more frequently at certain times after transplantation (see Chapter 11, Figure 11.1). CMV is arguably the most common infection after renal transplantation. Infection occurs most often in the early post-transplantation period when patients are most immunosuppressed. Fortunately, the availability of effective antiviral therapy has greatly reduced its lethal potential. BK virus is a human polyomavirus that has emerged as a serious infection that can cause

graft dysfunction and, ultimately, graft failure (see Chapters 9 and 11). It is critical to identify BK virus because its morphologic characteristics can be confused with acute rejection and the therapeutic response is based on minimization of immunosuppression. Chronic liver disease, usually caused by viral hepatitis, is an important cause of post-transplantation mortality (see Chapter 12). Hepatitis C virus is the most common cause of hepatitis after renal transplantation. Influenza is an important cause of preventable morbidity and mortality after transplantation. Viral infections are associated with malignancy in the late post-transplantation period.

Bacterial infections are common in the late post-transplantation period because of underlying risk factors and immunosuppression. As previously discussed, the high prevalence of peripheral vascular disease among diabetic patients and other transplant recipients greatly increases the risk for cellulitis and life-threatening bacterial sepsis. Ischemic bowel disease can also lead to septic shock and death. Bladder dysfunction, caused by diabetes and other anatomic urologic abnormalities, combine with immunosuppression to increase the risk for urinary tract infections and gram-negative bacterial sepsis. Tuberculosis is common among high-risk populations.

Several other, potentially life-threatening opportunistic infections occur sporadically but are nevertheless relatively common in the late post-transplantation period. Examples include infection with *Pneumocystis carinii, Toxoplasma gondii, Nocardia* species, *Aspergillus* species, *Listeria monocytogenes, Candida* species, *Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis,* and *Blastomyces dermatitidis*. Infection with opportunistic organisms can present as pneumonia, meningitis, cellulitis, osteomyelitis, or generalized sepsis. Diagnosis requires a high index of suspicion and an aggressive diagnostic approach.

Malignancy

Malignancies are common after renal transplantation; they are also more common in chronic dialysis patients. The risk for transmission of malignancies from the donor is extremely low, and almost all malignancies arise *de novo* in the recipient. Much of our knowledge of the malignancy and transplantation association comes from large registries, such as the Israel Penn Transplant Tumor Registry and the Australia-New Zealand Dialysis and Transplant Registry (see Vajdic and colleagues and Feng and associates in “Selected Readings”). These data indicate that the incidence of noncutaneous malignancies in renal transplant recipients is as much as 3.5-fold higher than that of age-matched controls. This increase can be attributed to an increased incidence of most tumors. However, the observed-to-expected incidence (the standardized incidence ratio) is not uniform among different types of tumors. Some tumors, such as lung cancer, breast cancer in women, and prostate cancer in men, do not appear to be more common among renal transplant recipients than among the general population. Colon cancer and renal cell carcinoma are more common than in the general population, although renal cell carcinoma may be no more common than in

the dialysis population. The differences in the observed-to-expected

incidence of different malignancies are consistent with the notion that more than one mechanism may explain the increased incidence of cancer after renal transplantation.

Some malignancies are undoubtedly caused by viral infections. Viruses that may otherwise reside in the host without untoward complications may cause potentially lethal malignant transformations in immunocompromised renal transplant recipients. Some of the tumors that occur with the highest incidence, compared with the general population, have possible viral causes. For example, PTLD has been linked to infection caused by EBV. Human herpesvirus-8 has been implicated in the high incidence of Kaposi sarcoma after renal transplantation. Human papillomavirus has been implicated in the pathogenesis of squamous cell cancer of the skin, vulva, vagina, and possibly uterine cervix. Liver cancer may be caused by chronic infection with hepatitis B and C viruses.

Urinary malignancies may occur more frequently among renal transplant recipients because renal disease may sometimes be associated with malignant and premalignant conditions such as acquired cystic disease of the native kidneys. Similarly, an increased risk for the rarely occurring parathyroid cancer may be attributable to long-standing renal disease and events occurring before transplantation.

Other mechanisms are undoubtedly at play. Immunosuppressive agents may damage DNA and lead to malignant transformation of cells and may also inhibit normal immune surveillance and thereby allow cells that have undergone malignant transformation to grow and divide unchecked. In an animal model, cyclosporine has been shown to promote cancer progression by a direct TGF-ß-related cellular effect that is independent of the host's immune cells. The antiproliferative effect of sirolimus may theoretically protect against tumor development and progression, although the clinical significance of this observation has yet to be confirmed (see Chapter 5, Part I).

Malignancies may occur at any time after transplantation. However, some are more likely than others to occur early after transplantation. These include PTLD (relatively common) and Kaposi sarcoma (relatively rare). Most other tumors tend to occur later. In the Australia-New Zealand Dialysis and Transplantation Registry, the mean time to the diagnosis of non-Hodgkin lymphoma (PTLD) was 8 to 10 years after transplantation. Moreover, the incidence of malignant tumors continues to increase throughout the late post-transplantation period. The cumulative incidence of noncutaneous malignancies is about 33% by 30 years after transplantation. The cumulative incidence of skin cancer is much higher, but few patients die of skin cancer after renal transplantation.

It is the cumulative effects of immunosuppression per se, rather than any particular agent or agents, that is principally responsible for the increased incidence of noncutaneous malignancies after renal transplantation. Age increases the risk for post-transplantation tumors, and it may be wise to minimize the amount of immunosuppression used in transplant recipients older than 60 or 65 years of age.

Cigarette smoking is also associated with a higher risk for post-transplantation malignancies.

Tumor markers, carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), and CA15-3 have a low specificity and sensitivity as screeners for malignancies in renal transplant recipients. The value of routine screening of the transplant population for common cancers (breast, colorectal, prostate) has been questioned; the risk-to-benefit ratio of such screening may be less favorable in the transplant population than in the general population because the life expectancy of transplant patients is intrinsically limited. Decisions regarding cancer screening should be made on an individual basis.

CHRONIC ALLOGRAFT FAILURE

CAF is second only to death with a functioning allograft function as the most common cause of late allograft failure. About 2.6% of grafts are lost annually to CAF. The etiology of CAF includes factors that can be considered either immune, or alloantigen dependent, and nonimmune, or alloantigen independent (Table 10.1). The distinction between alloantigen-dependent and alloantigen-independent factors is a convenient one, but multiple factors often coexist, and early events may program later events. For example, ischemic injury may make the graft more susceptible to acute rejection, and graft survival is impaired in the presence of hypertension. The pathologic features of CAF are described in Chapter 14.

Clinically, CAF presents as declining allograft function, often with proteinuria and hypertension. The clinical course may be unpredictable, and the biopsy findings in CAF are often poor predictors of the subsequent clinical course, particularly if the histologic findings are mild. Functional studies tend to underestimate the extent of morphologic injury. Patients with transplant glomerulopathy or severe arterial lesions on biopsy often have progressive declines in renal function. The chronic allograft disease index (CADI) described in Chapter 14 is an attempt to improve the prognostic value of the biopsy findings of CAN.

In Chapter 14, the argument is made to avoid using the familiar term *chronic allograft nephropathy* because there is no such specific lesion, and every attempt should be made by the pathologist to identify the predominant lesion that is affecting graft function. CAF can be considered to represent the cumulative and incremental damage from time-dependent immunologic and nonimmunologic causes.

Alloantigen-Dependent Risk Factors

The most convincing evidence that alloantigen-dependent factors are an important cause of graft loss comes from epidemiologic studies demonstrating an association between acute and chronic rejection. There is now little doubt that patients who have acute rejection episodes are more likely than patients with no acute rejection to

develop CAF; an episode of acute rejection in the first 6 months after transplantation increases the risk for late graft loss by up to 50%. Not all acute rejection episodes, however, lead to CAF, and it is difficult in individual patients with acute rejection to predict the likelihood of developing CAF. Acute rejections that occur late (after the first 3 months) appear to be more predictive of CAF than those that occur during the first 3 months; rejections that occur very early and are reversed may have little or no effect on outcome. It is unclear, however, whether acute rejection episodes that occur late because of attempts to withdraw immunosuppressive agents are as predictive of CAF as those that occur late on full doses of immunosuppression. It is clear that acute rejections that are more severe, either by histology or by increase in serum creatinine, are also more likely than less acute, severe rejections to herald CAF. Multiple acute rejections also appear to be more predictive of CAF.

The number of major histocompatibility complex (MHC) antigens that are mismatched between the recipient and donor is associated late allograft failure (see Chapter 3, Fig. 3.3). Deceased donor kidney transplants that have zero MHC mismatches have the best long-term allograft survival. Less marked are differences in late allograft survival between kidneys that have one to six MHC mismatches. The effect of MHC mismatches on graft half-life is further evidence that alloantigen-dependent factors are important in the pathogenesis of CAF.

Studies have also found an association between detection of preformed antibodies (see Chapter 3) at the time of transplantation and subsequent CAF. In some studies, the absence of preformed antibodies has correlated with

---

long-term allograft survival. Anti-HLA antibodies are consistently detectable in the months before recognition of chronic rejection, although their finding does not accurately predict its development. This observation, together with the widespread application of the C4d stain (see Chapter 9) in the evaluation of renal transplant biopsy specimens, has enhanced the emphasis of the role of ongoing humoral injury in CAF. In some studies, up to 60% of patients with CAF show evidence of antibody-mediated injury. The therapeutic implications of this finding are discussed in Chapter 5, Part V.

If it could be shown that higher doses of immunosuppression prevented CAF, this would be further evidence that alloantigen-dependent factors are important. Data showing that higher doses or more potent immunosuppression reduces the incidence of CAF, however, are equivocal. It is noteworthy that the introduction of cyclosporine in the 1980s led to dramatic (25% to 30%) reductions in the rate of acute rejection early after transplantation and greatly improved 1-year graft survival in most programs. However, there has been minimal improvement in graft half-life, suggesting that cyclosporine has had little net effect on CAF. The nephrotoxicity of the CNIs may have canceled the benefit that a reduced incidence of acute rejection from the use of CNIs may have had on CAF. In the 1990s, this trend may have abated with the more judicious use of the CNIs and the availability of non-nephrotoxic immunosuppressive agents. The use of mycophenolate mofetil for at least 1 year after transplantation has been reported to

reduce the incidence of CAF.

Several studies show that poor adherence to medications increases the likelihood of late graft failure, presumably from CAF. This, too, has been cited as evidence supporting the hypothesis that CAF is caused by alloantigen-dependent factors. These same patients are likely to be nonadherent with follow-up visits, limiting the ability to detect treatable acute rejection and increasing the risk for CAF. Patients who are nonadherent with immunosuppression, however, may also be nonadherent with antihypertensive agents, as well as other medications, which could increase the risk for CAF. Thus, it is difficult to attribute the adverse consequences of nonadherence entirely to alloantigen-dependent mechanisms.

Alloantigen-Independent Risk Factors

Patients with delayed, or “slow,” graft function have a higher rate of late allograft failure. The serum creatinine level at the time of discharge from hospital is a predictor of late graft loss (see Chapter 9). One theory holds that ischemic injury and delayed graft function result in a reduced number of functioning nephrons and that inadequate “nephron dosing” causes late allograft failure. However, delayed graft function is also associated with an increased incidence of acute rejection that could also explain its adverse effects on late graft survival. If true, this might suggest that close surveillance of patients for acute rejection during and after periods of delayed graft function could reduce the rate of late allograft failure.

Donor age is clearly associated with a higher rate of late allograft failure. Expanded criteria donor kidneys are defined by their higher incidence of late graft loss (see Chapter 4). Many of the histologic characteristics of CAF are similar to those seen in normal aging. It is unclear exactly how age of the kidney increases the risk for late allograft failure. The inadequate number of nephrons may create a physiologic response that sets in motion mechanisms ultimately leading to graft failure. The accelerated senescence theory proposes that the intrinsic age of the kidney (genetically determined in every cell and expressed in telomere length) limits its longevity in the recipient; the aging process is further accelerated by the repeated injury and stress represented by the alloantigen-dependent and alloantigen-independent factors discussed previously. By whatever mechanisms, the use of older kidneys appears to be a major cause of CAF.

A test of the hypothesis that inadequate nephron dosing may lead to CAF is to determine whether the size of the kidney affects long-term outcomes. Clearly, larger kidneys have a proportionally greater filtration capacity (although not necessarily a greater number of nephrons) than smaller kidneys. It has been theorized that placing a small kidney into a large recipient may create a situation of inadequate nephron dosing for that recipient and thereby precipitate CAF. A number of studies, however, have failed to demonstrate that this donor-recipient size mismatching increases the risk for CAF or late allograft failure.

The CNIs are nephrotoxic. The histologic changes of chronic CNI toxicity are described in Chapter 14. The extent of interstitial fibrosis that is a feature of CAF and CNI toxicity has been correlated to the expression of TGF-ß messenger RNA, which, in turn, may be stimulated by cyclosporine. Therefore, chronic CNI toxicity could be yet another alloantigen-independent mechanism contributing to the pathogenesis of CAF. Morphologic lesions attributable to chronic CNI toxicity are nearly universal in long-functioning grafts. The fact that graft survival has not been reduced by the increased incidence of acute rejections after cyclosporine withdrawal in randomized, controlled trials may be a result of the offsetting effects of nephrotoxicity in the controls continuing to take cyclosporine in these studies. Withdrawing cyclosporine may produce a tradeoff between the adverse effects of acute rejection and the beneficial effects of reduced nephrotoxicity, the net result being no difference in allograft survival. Additional studies with long-term follow-up are needed to confirm this hypothesis. A compromise clinical solution is to use low doses and levels of the CNIs in the long-term with the addition of an adjunctive agent, typically MMF (see Chapter 5, Part IV).

A distinctive histologic characteristic of CAF is the fibrointimal proliferation seen in arteries. In some ways, this vasculopathy resembles accelerated atherosclerosis, prompting investigators to consider whether alloantigen-independent risk factors for atherosclerotic vascular disease may also be risk factors for CAF. In heart transplant recipients, statins reduced graft vasculopathy. As yet, there are no studies in renal transplant recipients demonstrating that lipidlowering agents reduce CAF. Advanced glycation end products and oxidative stress, which have been implicated in the pathogenesis of atherosclerosis and the progression of renal disease, are increased in CAF to a degree that cannot be explained by renal dysfunction alone.

Registry data show that elevated blood pressure is also associated with graft failure. Of course, it is plausible that graft dysfunction causes hypertension, rather than hypertension causing graft dysfunction. Unfortunately, there are no randomized trial results to determine whether aggressive blood pressure lowering will reduce the rate of late graft failure. Cigarette smoking is another risk factor that could have a negative effect on graft vasculopathy and contribute to CAF. Homocysteine may be injurious to vascular endothelial cells, and transplant recipients have increased levels of plasma homocysteine compared with controls. Reduced renal function itself, however, is known to cause higher levels of homocysteine, and there are no data suggesting that reducing homocysteine improves graft survival. Similarly, oxygen free radicals are of theoretical importance in the pathogenesis of systemic atherosclerosis and could also play a role in endothelial injury and vasculopathy. Finally, infections have long been considered a possible mechanism in the pathogenesis of systemic atherosclerosis. If true, the increased incidence of CMV and other infections could also contribute to the vasculopathy of CAF. To date, the evidence that infections contribute to CAF is largely circumstantial.

The incidence of persistent proteinuria after transplantation (more than 1 to 2 g per 24

hours for longer than 6 months) has been estimated to be about 20% and tends to be greater with longer duration of follow-up. Proteinuria is an important risk factor for graft loss. Proteinuria causes interstitial nephritis in experimental animals, and studies in humans with renal disease have consistently reported that the amount of urine protein excretion predicts renal disease progression. Thus, it is possible that proteinuria could cause tubulointerstitial damage and contribute to CAF.

Renal Function Predicts Renal Function

Whatever the mechanisms underlying CAF, the bottom line remains the same: the better and more stable the graft function, the better the long-term outcome. The serum creatinine measured at varying stages after transplantation (at discharge from hospital; 6 months; 1 year) is a valuable predictor of long-term outcome, and events occurring in the first year are critical for long-term survival. Renal function is a better predictor of graft survival than the incidence of acute rejection, delayed graft function, HLA mismatch, and other risk factors. There has been a trend to improved renal function in the U.S. transplant population. Patients with a 1-year creatinine of less than 1.5 mg/dL and a change of creatinine of less than 0.3 mg/dL can look forward to excellent long-term graft outcome. Higher values are accompanied by a steadily increasing risk of graft loss (Fig. 10.3).

ACUTE REJECTION IN THE LATE POST-TRANSPLANTATION PERIOD

A small proportion of renal allografts are lost to acute rejection in the late post-transplantation period. Noncompliance with immunosuppressive medications may play an important role in some, if not most, late acute rejections, and should always be considered when they occur. Because many patients do not admit to missing doses of medications, it is difficult to know how often noncompliance causes acute rejection and graft failure. Transplantation centers frequently attempt to reduce doses of immunosuppression, replace drugs with less toxic or less expensive alternatives, or withdraw an agent to convert stable patients from triple to double immunosuppressive therapy. Such changes in immunosuppression are always associated with some risk for acute rejection. If patients are monitored closely, acute rejection can be detected early and can usually be treated successfully. On the other hand, if acute rejection goes undetected, as is often the case with nonadherent patients, it can cause or accelerate graft failure. The treatment of late acute rejection episodes is discussed in Chapter 5.

RECURRENT AND *DE NOVO* RENAL DISEASE

The problem of recurrent glomerulonephritis after transplantation is largely an unsolved one. The reported incidence of recurrence of the original renal disease in the allograft is variable, as is the resultant risk for graft failure. This variable incidence is reflected in the wide ranges noted in Table 7.4 (see Chapter 7). Much of the variation is

based on differences in the duration of follow-up and on differences in the frequency with which patients undergo biopsies. It is probable that as graft failures from death and rejection decline, the apparent incidence of graft failure from recurrent disease will increase. It is also frequently difficult to establish whether some diseases represent recurrences or *de novo* glomerular disease. For patients who did not have a specific biopsy diagnosis of the cause of their native kidney disease, the diagnosis may become evident in the pathology of their transplant biopsy.

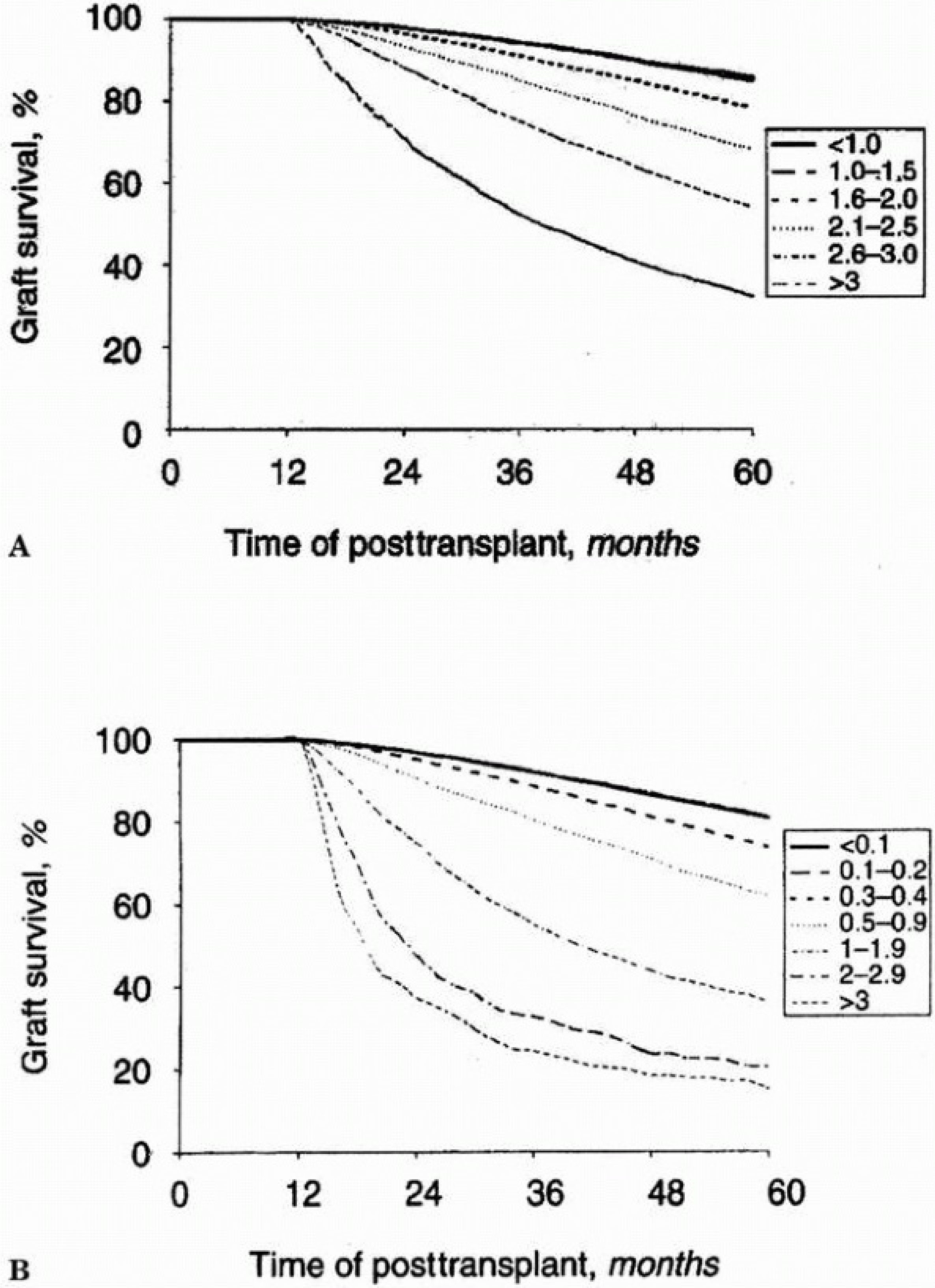


FIGURE 10.3 Relationship of serum creatinine (mg/dL) (**A**) and change of serum creatinine (mg/dL) (**B**) 1 year after transplantation to long-term graft function. (From Hariharan S, McBride M, Cherikh W, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 2002;62:311-318, with permission.)

The incidence of recurrent and *de novo* disease among a large cohort in the Renal Allograft Disease Registry was 3.4% over a mean follow-up period of 5.4 years. Diagnoses were focal segmental glomerulosclerosis (FSGS) (34.1% of the total), immunoglobulin A (IgA) nephropathy (13.2%), diabetes (11.4%), membranoproliferative glomerulonephritis (MPGN) (10.8%), membranous nephropathy (9.6%), hemolytic uremic syndrome or thrombotic thrombocytopenic purpura (4.8%), and other (16.1%). There was a significant increase in graft failures among the recurrent and *de novo* disease groups (55%) when compared with the others (25%; $P < .001$). In contrast, in a small cohort of two-haplotype-matched living related donor transplants followed for a mean of 8.3 years, the incidence of recurrent disease was 15%, and was 27% in patients with glomerulonephritis as the original kidney disease. The higher incidence of disease recurrence in the latter study may reflect the lack of competing graft loss to rejection in well-matched recipients exposed to relatively long follow-up.

In data from large registries, it may be more difficult to discern the incidence of disease recurrence than to define the outcome of patients after recurrent disease has been diagnosed. However, in a group of more than 1500 Australian patients with biopsy-proven glomerulonephritis who were followed for 10 years, the incidence of graft loss as a consequence of any kind of glomerulonephritis was 8.4%. FSGS is clearly the form of glomerular disease most commonly associated with recurrence and graft loss, and patients who have lost a prior transplant because of recurrent FSGS are at much higher risk. Early recognition of recurrent FSGS is particularly important because it may respond to plasmapheresis. The prevention and management of recurrent FSGS, which is most common in children, is discussed in detail in Chapter 16. MPGN type 2 (dense-deposit disease) recurs in almost 100% of patients and often leads to graft failure. MPGN type 1 recurs in about 20% to 30% of patients and leads to graft failure in about 50%. Membranous glomerulonephritis can present as *de novo* disease but probably recurs in 5% to 10% of patients. About 25% of patients may ultimately lose their grafts from recurrent membranous nephropathy. Histologic recurrence of IgA nephropathy is common. Allograft failure to IgA nephropathy is higher than once reported and may be as high as 25%. Henoch-Schönlein purpura recurs in a high proportion of patients and leads to graft failure in about 25%. Antiglomerular basement membrane disease recurs in 10% to 25% of patients but rarely causes graft failure. Diabetes recurs histologically in 100% of patients after a few years. Graft failure as a consequence of diabetes occurs in about 5% to 10% patients, but this percentage may increase as graft failure caused by rejection declines.

ROLE OF NONADHERENCE IN LATE ALLOGRAFT FAILURE

The frequency of nonadherence with immunosuppressive medications is difficult to measure, but it is probably more frequent than reported. As a group, transplant recipients may be especially reluctant to admit to nonadherence if they believe that doing so might jeopardize their chances of ever receiving another transplant. Some

patients may admit to nonadherence and seek financial assistance in obtaining their medications (see Chapter 19). Nonadherence may also manifest as a failure to keep scheduled appointments or as inconsistent immunosuppressant drug levels. Patients who fail to have their serum creatinine measurements performed regularly are more likely to have late graft failure.

Patients may become nonadherent with medications for a number or reasons (see Chapter 19, Table 19.2). They may harbor the false belief that taking medication regularly is unnecessary. This belief may be reinforced by several years of an uneventful post-transplantation course. Many patients believe that the effects of immunosuppression continue indefinitely, even when doses of medications are missed. Such patients are more likely to be nonadherent than are patients who have a better understanding of the duration of the action of immunosuppressive medications. Some patients may become nonadherent because they fear the adverse effects of medication more than they fear graft rejection. This is particularly true of adolescents, who abhor the social stigma of the body habitus changes caused by corticosteroids and, to a lesser extent, cyclosporine.

Patients may simply forget to take doses of medication. In a survey of 100 members of the Transplant Recipient International Organization (TRIO), less than 30% were taking fewer than 5 medications, and 35% reported taking 10 to 20 different medications each day. Only 2% of the medications required a single daily dose. (In general, studies show that the number of times a day that patients must take medications is a stronger predictor of nonadherence than is the total number of medications.) Of those surveyed, 25% admitted missing doses of medications, and 55% of these gave forgetfulness as the reason. It is likely that the members of the TRIO represent a highly motivated population of transplant recipients. Only 35% of the participants were kidney transplant recipients, and recipients of other, nonrenal organs may suffer lethal consequences if their grafts fail.

Nonadherence increases the risk for late graft loss threefold to fivefold and may be the most common cause of late graft loss. Nonadherence can lead to graft failure through several different mechanisms. Patients who receive inadequate immunosuppression because of nonadherence may develop acute or chronic rejection that leads to graft failure. Nonadherence with clinic visits and laboratory follow-up can also contribute to late graft failure. Acute rejection in the late post-transplantation period rarely presents with signs and symptoms until it is far advanced. Thus, to be successfully treated, acute rejection must be detected early, which can only be done by detecting increases in serum creatinine levels soon after they occur. It follows that patients who do not see physicians and who do not have frequent measurements of serum creatinine levels are less likely to have rejection detected at an early stage, when it is treatable. It also follows that it is the responsibility of transplant physicians and transplantation team members to constantly reinforce to patients the importance of compliance and to make every effort to facilitate compliant behavior by minimizing the complexity of the

medication protocol and other aspects of long-term post-transplantation follow-up.

Selected Readings

Part I

Bath-Hextall F, Leonardi-Bee J, Somchand N. Interventions for preventing non-melanoma skin cancers in high-risk groups. Cochrane Library 2009;1:1-35.

Bruno S, Remuzzi G, Ruggeneti P. Transplant renal artery stenosis. J Am Soc Nephrol 2004;15:134-141.

Bustami R, Ojo AO, Wolfe R, et al. Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. Am J Transplant 2004;4:87-92.

Caillard S, Lelong C, Pessione F, et al. Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: report of 230 cases from the French registry. Am J Transplant 2006;6:2735-2742

Chabra D, Grafals M, Skaro A, et al. Impact of anemia on patient and graft survival and on rate of acute rejection. Clin J Am Soc Nephrol 2008;3:1168-1174

Cruz D, Brickel H, Wysolmerski J, et al. Treatment of osteoporosis and osteopenia in long-term renal transplant patients with alendronate. Am J Transplant 2002;2:62-67.

Campistol J, Albanell J, Arns W. Use of proliferation signal inhibitors in the management of post-transplant malignancies: clinical guidance. Nephrol Dial Transplant 2007;22(Suppl 1):36-41.

Danovitch G. Guidelines on the firing-line. Am J Transplant 2003;3:514-515.

Delgado P, Diaz JM, Silva I, et al. Unmasking glucose metabolism alterations in stable renal transplant recipients: a multicenter study. Clin J Am Soc Nephrol 2008;3:808-813.

El-Amm J, Doshi M, Singh A, et al. Preliminary experience with cinacalcet use in persistent secondary hyperparathyroidism after kidney transplantation. Transplantation 2007;83: 546-549.

Feng S, Buell JF, Chari R, et al. Tumors and transplantation: the 2003 third annual ASTS state of the art winter symposium. Am J Transplant 2003;3:1481-1487.

Kasiske B, Cosio FG, Beto J, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report of the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant 2004;4(Suppl 7):13-53.

Palmer S, Stripolli GF, McGregor D. Interventions for preventing bone disease in kidney transplant recipients: a systematic review of randomized controlled trials. Am J Kidney Dis 2005;45:638-649.

Schena F, Pascoe M, Albaru J, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation 2009;87:233-242.

Shirali A, Bia M. Management of cardiovascular disease in renal transplant recipients. Clin J Am Soc Nephrol 2008;3:491-504.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) Hypertension. 2003;42:1206-1292.

Vajdic C, McDonald S, McCredie M, et al. Cancer incidence before and after kidney transplantation. JAMA 2006,296:2823-2831.

Villeneuve P, Schaubel D, Fenton S. Cancer incidence among Canadian kidney transplant recipients. Am J Transplant 2007; 7:941-948

Vincenti F, Friman S, Scheuermann L, et al. Results of an international randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant 2007;7:1506-1514.

Part II

Briganti E, Russ G, McNeil J, et al. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med 2002;347:103-107.

Cosio F, Hickson L, Griffin M, et al. Patient survival and cardiovascular risk after kidney transplantation: the challenge of diabetes. Am J Transplant 2008;8:593-599.

Fellsrom B, Holdaas H, Jardine A, et al. Effect of fluvastatin on renal end points in the Assessment of Lescol in Renal Transplant (ALERT) trial. Kidney Int 2004:66:1549-1555.

Golgert W, Appel G, Hariharan S. Recurrent glomerulonephritis after renal transplantation: an unsolved problem. Clin J Am Soc Nephrol 2008;3:800-807.

Gourishankar S, Hunsicker L, Jhangri G, et al. The stability of the glomerular filtration rate after renal transplantation is improving. J Am Soc Nephrol 2003;14:2387.

Hariharan S, McBride M, Cherikh W, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 2002;62:311-318.

Ivanyi B. A primer on recurrent and de novo glomerulonephritis in renal; allografts. Nat Clin Prac Nephrol 2008:4;446-456.

Karthikeyan V, Karpinski J, Nair R, et al. The burden of chronic kidney disease in renal transplant recipients. Am J Transplant 2003;4:262-269.

Kasiske B, Vazquez MA, Harmon WE, et al. Recommendations for the outpatient surveillance of renal allograft recipients. J Am Soc Nephrol 2000;11(Suppl 15):1.

Pascual M, Theruvath T, Kawai T, et al. Strategies to improve long-term outcomes after renal transplantation. N Engl J Med 2002;346:580-590.

Perico N, Gaspari F, Remuzzi G. Assessing renal function by GFR prediction equations in kidney transplantation. Am J Transplant 2005;5:2698-2703.

Solez K, Colvin RB, Racusesn L, et al. Banff '05 Meeting Report. Differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy (CAN). Am J Transplant 2007;7:518-526.

Wilkinson A. Use of angiotensin-converting enzyme inhibitors and angiotensin II antagonists in renal transplantation: delaying the progression of chronic allograft nephropathy? Transplantation Rev 2000;14:138-143.

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

11

Infections in Kidney Transplantation

David A. Pegues

Bernard M. Kubak

Cynthia L. Maree

Aric L. Gregson

Kidney transplantation is associated with lower risk for infection than other solid organ transplantations, reflecting the elective nature of kidney transplantation and clinical and nutritional status of recipients. Infection however, remains a significant cause of morbidity and mortality in renal transplant recipients. Infections related to transplant surgical complications, acquisition of health care-associated pathogens, and reactivation of latent disease can affect graft function and transplant outcome. Graft dysfunction or chronic rejection leads to augmented immunosuppression, increasing the risk for infection with immunomodulating viruses. Infectious syndromes encountered in the kidney transplant recipients include device-associated infections, genitourinary infections, pneumonia, and disseminated or organ-specific viral diseases.

This chapter highlights the infectious disease issues in kidney transplant recipients, post-transplantation infection prophylaxis, and the recognition and treatment of common and emerging infectious syndromes with appropriate antimicrobial therapy to minimize allograft toxicity. As an invaluable resource document, readers are also referred to Green and colleagues (see "Selected Readings").

GENERAL GUIDELINES FOR INFECTION RECOGNITION

Table 11.1 summarizes the risk factors for infection in the pretransplantation and post-transplantation periods. Recognition of the following factors may assist in the identification of the causative pathogen and the initiation of appropriate empiric antimicrobial therapy before laboratory confirmation:

1. The *timing of an infectious episode after transplantation* is critical. Most infections occur in the first month after transplantation and are typically related to technical complications of the surgery or invasive medical devices and most commonly involve the genitourinary infection.

During months 1 to 6, infections associated with postoperative complications or with enhanced immunosuppression can develop, persist, or recur. Augmented immunosuppression is associated with an increased risk for infection with immunomodulating viruses such as cytomegalovirus (CMV), human herpesvirus (HHV), hepatitis B virus (HBV), hepatitis C virus (HCV), and Epstein-Barr virus (EBV), that enhance susceptibility to opportunistic infections by altering the expression of inflammatory mediators and cytokines by a complex interrelated cascade. This leads to a permissive environment for opportunistic pathogens such as *Pneumocystis*, *Aspergillus*, *Cryptococcus*, and other fungi; bacteria including *Listeria monocytogenes*; and *Nocardia*, *Toxoplasma*, and other viruses. CMV and other HHVs also exert an immunomodulating effect that has been implicated in allograft rejection, obliterative transplant arteriopathy, and post-transplantation lymphoproliferative disorder (PTLD).

TABLE 11.1 Risk Factors for Infection in Renal Transplant Recipients

Pretransplantation (Recipient)

- Medical conditions (renal failure, diabetes, malnutrition, disorders of immune function)
- Immunosuppression for chronic conditions (corticosteroids, cyclophosphamide)
- Unrecognized or inadequately treated infection in the recipient
- Colonization with unusual or resistant organisms (e.g., VRE in stool, MRSA in nares or on skin, drug-resistant Enterobacteriaceae or *Pseudomonas* in genitourinary tract, gastrointestinal tract, and upper respiratory tract; acquisition of yeasts on mucocutaneous and other mucosal surfaces; yeasts or molds on skin, mucosal surfaces)

- Preoperative antibiotic exposures (e.g., increased infection risk for Clostridium difficile and antibiotic resistant organisms)

- Duration and frequency of hospitalizations

Perioperative

- Complexity of surgery and requirement for re-exploration

- Prolonged operative time

- Graft injury or prolonged ischemia; acute graft failure

- Bleeding or multiple blood transfusions

- Graft infection (donor) or unrecognized infection in the donor

- Perioperative bacteremia or sepsis

- Microbial contamination of preservation fluid of graft

- Retained foreign bodies

Post-transplantation

- Acute graft failure or dysfunction; requirements for augmented immunosuppression and prolonged cytolytic therapies
- Early re-exploration or retransplantation
- Complicated postoperative management; development or worsening of comorbid medical conditions (hyperglycemia, hepatic disease, respiratory insufficiency, altered sensorium)
- Infection with immunomodulating viruses (CMV, HHV, respiratory viruses)
- Prolonged catheters, genitourinary stents, or mechanical ventilation
- Bladder-drained procedure; enteric-drained procedure (pancreas, kidney-pancreas transplantation), pancreas transplantation after kidney transplantation
- Anastomotic breakdown or leaks; development of fluid collections, devitalized tissues, hematomas

- Leukopenia, thrombocytopenia, acquired hypogammaglobulinemia
- Prolonged antibiotic therapy; acquisition of antibiotic-resistant health care pathogens
- Corticosteroids: maintenance dose and pulses
- Hospital exposures: construction, ventilation, and water supply
- Selected occupational, gardening, and recreational activities: composting, exposure to decaying vegetation, hunting
- Lack of appropriate hand hygiene by caregivers
- Marijuana use

CMV, cytomegalovirus; HHV, human herpesvirus; MRSA, methicillin-resistant *Staphylococcus aureus;* VRE, vancomycin-resistant *Enterococcus*.

After post-transplantation month 6, patients generally can be categorized as those with successful graft outcome and minimal long-term maintenance immunosuppression, those with poor graft function because of chronic rejection who require intensified immunosuppression, and those chronically infected with immunomodulating viruses such as CMV. Infections in patients with long-term successful allografts are typically similar to those that develop in persons in the community, whereas the latter two patient groups are at ongoing risk for opportunistic infections.

2. The *net state of immunosuppression* is a semiquantitative assessment that reflects the complex interaction of the following factors:

- The dose, duration, and temporal sequence of immunosuppressive therapy, including augmented immunosuppression for episodes of rejection
- Quantitative immunodeficiency, including leukopenia, thrombocytopenia, and low immunoglobulin levels
- Breach of tissue barriers by foreign bodies (e.g., urinary and venous catheters, ureteral stents), open wounds, fluid collections, and devitalized tissues
- Metabolic abnormalities such as hyperglycemia, uremia, liver failure, and malnutrition
- Infection with immunomodulatory viruses

3. The *infectious history of the donor,* specifically any infectious syndromes and pathogen that can be directly transmitted with the allograft.

4. *Recipient history of infections and exposures,* such as tuberculosis, hepatitis viruses, human immunodeficiency virus (HIV), varicella-zoster virus (VZV), CMV, or EBV; immune-altering conditions, such as surgery or functional asplenia; and pretransplantation medical conditions including rheumatologic disorders, such as systemic lupus erythematosus, that require immunosuppressive therapy, diabetes mellitus, substance or injection drug use, liver dysfunction, malnutrition, and potential risk for exposure to geographically restricted endemic mycoses, toxoplasmosis, tuberculosis, and *Strongyloides* species.

5. The *acquisition of community and health care-associated pathogens,* such as *Streptococcus pneumoniae,* Enterobacteriaceae, and *Pseudomonas* species, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE). Pretransplantation dialysis patients and kidney recipients may harbor bacteria and yeasts on their skin and sinopulmonary and gastrointestinal tracts related to frequent contact with health care settings and antimicrobial exposure. In the setting of graft dysfunction, postoperative surgical complications, or rejection, these colonizing organisms have the potential to cause invasive infection. Identifying these colonizing organisms and, when appropriate, determining antimicrobial susceptibility may help to direct empiric antimicrobial therapy if clinical infection develops.

6. *Factors that delay or confound the diagnosis of infection in the recipient* include an impaired host inflammatory response; the delay in clinical diagnosis because of the lack of classic clinical and radiologic signs associated with infection and inflammation compared with the immunocompetent host; the rapid progression of infections in this context, particularly with altered transplant anatomy; the failure to recognize high-risk patient characteristics (e.g., diabetes, enhanced and prolonged immunosuppression,

multiple antibiotic courses); and delays in laboratory diagnosis and limited rapid diagnostic assays for fungal, mycobacterial, and viral diseases.

PRETRANSPLANTATION SCREENING: DONOR AND CANDIDATE

Untreated or unrecognized infections in the recipient can become clinically apparent in the post-transplantation period. These can include intravascular

device infection, pneumonia, periodontal abscess, intra-abdominal, hepatobiliary, or genitourinary tract infection. During pretransplantation screening, the identification of latent or active infections in the recipient can lead to a reappraisal of transplant candidacy or to alterations in standard post-transplantation antimicrobial therapy. For the living related donor, a careful history of potential latent infections should be ascertained, and any active infection should be treated when appropriate. Donation should be deferred until the respective infection resolves.

It may be difficult to differentiate among an infection acquired from the allograft, from an exogenous source, or from reactivation of latent disease in the recipient. The following infectious agents have been implicated in transmission from the donor allograft: aerobic gram-positive and gram-negative bacteria, anaerobic bacteria, *Mycobacteria* species, *Toxoplasma* species, and *Strongyloides* species; HIV, CMV, HBV, HCV, herpes simplex virus (HSV), VZV, EBV, and West Nile virus; and fungi including *Candida* species, *Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans, Aspergillus* species, and *Scedosporium apiospermum*. Serious complications of donor allograft-transmitted infections include bacteremia, fungemia, disruption of the vascular anastomoses, formation of “mycotic” (microbial) aneurysms, and infective endocarditis. The risk for donor-transmitted infection can be reduced by careful screening and epidemiologic evaluation (see Chapter 7).

Donor Screening

Postoperative infections can arise from inadequate donor screening. The donor's medical and social history should include information on high-risk behaviors such as prior hospitalizations and blood transfusions, injection drug use, incarceration histories, and tuberculosis exposures. These exposures may be associated with an increased risk for acute HIV, HBV, and HCV infection where screening serologies may be negative. The organ procurement agency should provide results of donor microbiology cultures, serum serologies, and history of infections, including upper and lower urinary tract infection and bacteremia that may not be confirmed by the laboratory until after transplantation in some cases. Because many deceased donor kidneys may be recovered from patients in intensive care units, occult bacteremias or genitourinary tract infection should be excluded by appropriate cultures. In the case of donor-associated bacteremia, appropriate antimicrobial therapy should be administered to the recipient typically for 14 days, and follow-up blood cultures should be obtained to exclude endovascular

infection of the vascular anastomosis. Although rare, this complication has been associated with donor-derived bloodstream infection with *S. aureus, Pseudomonas aeruginosa,* other gram-negative bacilli, and *Candida* and *Aspergillus* species. During the allograft harvesting and transplantation, microbial contamination of the preservation media can occur. In such cases, appropriate antimicrobial therapy should be administered to the recipient, typically for 14 days. Syphilis has been transmitted in solid organ transplantations but is not a contraindication to organ donation. The recipient should receive treatment appropriate to the presumed stage of donor syphilis infection. Deceased donor kidneys have been transplanted successfully from donors with localized, nongenitourinary infections, including pneumonia and meningitis. However, donors with active fungal infection, especially bloodstream and genitourinary infections, unspecified viral infections, suspicion of encephalitis, or ambiguous causes of infectious death should be avoided. A nucleic acid amplification technique (NAT) is now being used more commonly to screen donor blood for HBV, HCV, and HIV-1 and -2 and should reduce the risk for transmission of these viral agents during the “window” period to negligible.

Transplant Candidate Screening

Evaluation of the transplant candidate for infection risk should include a history of antibiotic allergies and nature of reaction, a dental examination, and assessment for remote or active infection, including a urine culture and chest radiograph (Table 11.2). Patients with polycystic kidney disease who have been treated for infected polycystic kidneys should have repeatedly negative urine cultures. Pretransplantation polycystic nephrectomy is occasionally required (see Chapter 7).

The candidate should be evaluated for potential risk for exposure to *Mycobacterium tuberculosis* or endemic mycoses, including history of prior residence or travel to high-risk areas, PPD skin test, blood interferon-gamma release assay, and, if indicated, serologic testing for *C. immitis* or *H. capsulatum,* especially if the chest radiograph demonstrated calcified or noncalcified granuloma. Living donors should have a PPD skin test, and urine acid-fast bacillus (AFB) stain and mycobacterial cultures should be obtained if there is a history compatible with disseminated tuberculosis. The higher incidence of cutaneous anergy in patients with end-stage renal disease may confound the tuberculosis risk assessment, so it is critical to assess for a history of latent or active tuberculosis or compatible chest radiograph and to administer isoniazid prophylaxis, if indicated. The 2000 American Thoracic Society and Centers for Disease Control and Prevention (CDC) guideline recommends treatment of latent tuberculosis with isoniazid (5 mg/kg per day, maximum of 300 mg daily for adults) for 9 months. Patients who previously completed an adequate treatment course for latent or active tuberculosis typically do not require additional antituberculous therapy after transplantation.

TABLE 11.2 Transplant Candidate Screening

Underlying medical conditions (see Chapter 7)

Antibiotic and medication allergies and adverse reactions

Chest radiograph (e.g., any evidence of active infiltrates; old granulomatous lesions; scarring)

Dental assessment

History of sexually transmitted diseases, high-risk behaviors, injection drug usage

Purified protein derivative (PPD) skin test; history of tuberculosis risk factors and exposures

Urine culture

Routine serologic testing:

- Cytomegalovirus (CMV) IgG antibody

Epstein-Barr Virus (EBV) antibody panel

Herpes simplex virus (HSV) and varicella-zoster virus (VZV) IgG antibodies

Hepatitis B virus (HBV) surface antigen (HBsAg), core antibody (HBcAb IgM and IgG), surface antibody (HBsAb)

Hepatitis C virus (HCV) IgG antibody

HIV 1 and 2 antibody

Rapid plasma reagin (RPR) or TP-PA (Treponema pallidum particle agglutination) test for syphilis

Special serologic testing (based on epidemiologic risk factor or exposure history):

Coccidioides IgM and IgG antibody by enzyme immunosorbent assay (EIA)

Histoplasma immunodiffusion antibody or urine antigen

Human T-cell lymphotropic virus (HTLV-I/II) antibody

Strongyloides antibody
Trypanosoma cruzi antibody

Preoperative antibody testing, when appropriate, should include CMV, VZV, EBV, HSV-1 and -2, HIV-1 and -2; anti-hepatitis B virus surface antibody (anti-HBsAb), surface antigen (HBsAg), and core antibody (HBcAb); and HCV antibody (see Chapter 12); and testing for endemic mycoses when appropriate.

Specific Serologic Testing

Cytomegalovirus

The seroprevalence of CMV ranges from 40% to 97%, depending on the population screened, and increases with age. Most adult dialysis patients have detectable immunoglobulin G (IgG) antibody to CMV. The CMV antibody status of the donor and recipient should be ascertained. A CMV-seronegative recipient (R-) of a CMV-seropositive donor (D+) is at the highest risk for developing subsequent CMV infection and disease. After transplantation, these recipients require preemptive antiviral therapy, typically for 100 days, and careful clinical and laboratory monitoring for evidence of CMV viremia. Recipients receiving antilymphocytic therapy may require prolonged preemptive antiviral therapy. Although CMV-seropositive recipients (D+/R+, D-/R+) have a lower risk for CMV disease, a similar prevention strategy should be employed, based on the individual patient risk factors and net state of immunosuppression. The clinical implications of the CMV infection are discussed in "Viral Infections" and summarized in Table 11.3.

TABLE 11.3 Risk for CMV Infection and Disease without CMV Prophylaxis Donor and Recipient CMV Serostatus

	Cytomegalovirus Antibody Status				

Donor	Recipient	Terminology	Infection (%)	Disease (%)	Pneumoniti (%)
+	-	Primary infection	70-88	56-80	30
+	-	Reactivation	0-20	0-27	Rare
+	+*	Reactivation or superinfection	70	27-39	3-14
-	-		Zero†		
±	+	With antirejection, ALA plus conventional immunosuppression‡	—	65	—

* The source of infection and disease may be a new virus strain from the donor or latent virus in the recipient.

† Inadequate or incorrect donor-recipient screening, or viral acquisition during recent peritransplantation periods may result in false-negative serologies; in this case, recent serologies are recommended.

‡ Results with conventional immunosuppression: cyclosporine or tacrolimus, azathioprine (or mycophenolate mofetil), prednisone, and antilymphocyte antibody (ALA).

(Data from Davis CL. The prevention of cytomegalovirus disease in renal transplantation. Am J Kidney Dis 1990;16:175-188; Hartmann A, Sagedal, S, Hjelmesaeth, J. The natural course of cytomegalovirus infection and disease in renal transplant recipients. Transplantation 2006;82:S15-S17, with permission.)

Epstein-Barr Virus

Both EBV-seronegative recipients of grafts from EBV-seropositive donors and EBV-seropositive recipients may be at increased risk for PTLD, particularly if they receive prolonged or repeated courses of antilymphocytic therapy (see Chapter 10). EBV mismatch occurs more commonly in pediatric kidney recipients. In high-risk patients, the quantitative EBV viral load can be assayed by polymerase chain reaction (PCR).

Other Human Herpesviruses

Other HHVs of significance to organ transplant recipients include HSV-1 and -2, VZV, and HHV-6 and HHV-8. HHV-6 has been implicated as a cofactor for CMV and other infections; no treatments are available. HHV-8 may cause transplant-associated Kaposi sarcoma and EBV-negative lymphoproliferative disease. Generally, screening for HHV-6 and -8 is not performed before transplantation.

Hepatitis B and C

The detection of chronic HBV and HCV infection in both transplant donors and recipients has improved with newer laboratory methods to detect viral-specific antibodies, antigens, and nucleic acids. The impact of latent or active HBV and HCV infection on transplant candidacy and kidney donation is discussed in Chapter 12.

Human Immunodeficiency Virus

All potential transplant donors should be tested for HIV-1 and -2 antibody. A history of any high-risk behaviors must be obtained, because transplant-derived HIV infection has been associated with acute infection in the seronegative "window" period or associated with massive blood transfusion and false-negative donor HIV antibody test results (see Chapter 4). Routine donor HIV antibody testing routine donor HIV testing and rejection of organs from donors with a high-risk history have reduced the risk for infection to an almost negligible degree. However, in January 2007, four transplant recipients acquired HIV infection from a self-identified high-risk donor, the first instance of HIV transmission through organ donation in the United States since 1985. Routine NAT testing of donor blood would have detected acute HIV infection in this donor with acute HIV infection.

Human T-Lymphotrophic Viruses

Human T-lymphotrophic virus I (HTLV-1) is more common in individuals from the Caribbean and Japan. Blood products, organ transplants, and intimate contact can transmit HTLV-1. Clinical syndromes include HTLV-1-associated myelopathy or tropical spastic paraparesis and adult T-cell leukemia and lymphoma virus. HTLV-1 myelopathy has been reported after transplantation from an infected donor. HTLV-2 is serologically similar to HTLV-1, but disease association is under investigation. Donors with HTLV-1 seropositivity are generally not used.

West Nile Virus

West Nile virus (WNV) is a vector-borne flavivirus transmitted from the bite of an infected mosquito, and much less commonly through blood and transplanted organs. In late 2002, the CDC confirmed the transmission of WNV to organ recipients from a single donor with serious consequences to the recipients. First-generation serologic and PCR assays are available. The epidemiology of WNV has changed rapidly, so the extent of risk to the donor pool and recipients remains under investigation. During summer months, it is prudent to avoid organs from donors from an area with active WNV infection who have symptoms of a viral illness, especially encephalitis or meningitis.

Coccidioidomycosis and Histoplasmosis

Candidates who have resided in at-risk geographic areas should be tested for *C. immitis* IgM and IgG antibody by enzyme immunoassay (EIA) or *H. capsulatum* antibody by immunodiffusion during transplant evaluation. Because of the substantial risk for reactivation, recipients with a history of prior infection with endemic fungi or who have detectable antibodies should receive prophylactic azole antifungal therapy following renal transplantation typically for the life of the allograft.

Transplant Candidate and Recipient Immunization

Vaccine-preventable infections are a major source of morbidity following solid organ transplantation. During the transplant evaluation, the candidate's immunization history should be carefully reviewed and immunizations updated. Current adult and pediatric immunization schedules are available at http://www.cdc.gov/vaccines/recs/schedules/default.htm, and updated recommendations for vaccination of solid organ transplant recipients were published in 2007 and are summarized in Table 11.4.

Unless there are contraindications, VZV-seronegative transplant candidates should receive two doses of live varicella vaccine, and seropositive candidates 60 years or older should receive a single dose of live zoster vaccine to decrease the risk for varicella disease. Other live attenuated vaccines, such as measles, mumps, and rubella

(MMR) and varicella, should be administered no later than 4 to 6 weeks before transplantation to minimize the possibility of vaccinederived infection in the post-transplantation period. Ideally, household contacts of transplant recipients should be fully immunized to protect the transplant recipient. Live vaccines should be avoided before transplantation in candidates receiving immunosuppressive therapy and following solid organ transplantation. Other live attenuated vaccines, including bacille Calmette-Guerin, oral polio, and live attenuated influenza vaccine, should also be avoided.

Inactivated vaccines are safe to administer to transplant recipients and include hepatitis A and hepatitis B, intramuscular influenza A and B, 23-valent unconjugated and 7-valent conjugated pneumococcal, *Haemophilus influenzae* B, inactivated polio, diphtheria-acellular pertussis-tetanus (Tdap), and polysaccharide or conjugated meningococcal vaccines. Annual influenza vaccination is recommended for transplant candidates and recipients. The anecdotal risk rejection with influenza immunization has not been substantiated in randomized trials of solid organ transplant recipients, whereas influenza infection in these patients is associated with higher morbidity and mortality, graft rejection, and prolonged viral shedding. Immunization with meningococcal and inactivated polio vaccines may be appropriate for special risk situations, including travel or occupational risk. An accelerated schedule for hepatitis B immunization can be used before and following transplantation, especially if the organ is from a donor with anti-HBsAb. Following hepatitis B immunization, anti-HBsAb levels should be measured to document seroconversion.

PATHOGENESIS AND DIAGNOSIS OF INFECTION IN KIDNEY ALLOGRAFT RECIPIENTS

About 80% of infections in kidney transplant recipients are bacterial. Tables 11.5 and 11.6 summarize the syndromes and microbial pathogens commonly encountered in kidney transplant recipients. Infections occurring during the first month are typically associated with technical complications of the surgery or indwelling medical devices and most commonly include genitourinary tract infection, bacteremia, surgical site infection, pneumonia and intra-abdominal infection.

TABLE 11.4 Recommended Immunizations for Pediatric and Adult Tra Recipients

Vaccine	Inactivated/Live Attenuated	Pediatric/Adult (P/A)	Recommended Before	Reco After

	(I/LA)		Transplantation	Tran
Haemophilus influenzae b	I	P	Yes	Yes
Hepatitis B	I	P/A	Yes	Yes
Hepatitis A	I	P/A	Yes	Yes
Human papillomavirus	I	P/A	Yes	Yes
Influenza, injected	I	P/A	Yes	Yes
Measles, mumps, rubella (MMR)	LA	P	Yes	No
Meningococcal (conjugated or polysaccharide vaccine)	I/I	P/A	Yes	Yes
Polio, inactivated	I	P	Yes	Yes

S. pneumoniae (conjugated or polysaccharide vaccine)	I/I	P/A	Yes	Yes
Tetanus, diphtheria, acellular pertussis (Td/Tdap)	I	P/A	Yes	Yes
Varicella	LA	P/A	Yes	No
Zoster	LA	A	Yes	No

[1] Indicated for adults with anatomic or functional asplenia or terminal complement preadolescents, first-year college students living in dormitories, and others determi

[2] Children older than 5 years should receive 23-valent pneumococcal polysaccharide Children younger than 2 years should receive 3 doses of conjugated pneumococcal v should be repeated regularly (every 3-5 years) after transplantation.

[3] Tdap (Adacel) should replace a single dose of Td for adults younger than 65 years w received a dose of Tdap.

[4] Children and nonimmune adults should receive two doses of varicella vaccine (Var

[5] Adults older than 60 years should receive a single dose of zoster vaccine (Zostivax)

TABLE 11.5 Commonly Encountered Bacterial Pathogens in Renal Trar

Intra-abdominal	Septicemia	Urinary Tract	Pneumonia
Enterobacteriaceae *Enterococcus* sp. Anaerobes (*Bacteroides* sp.)	Enterobacteriaceae *Pseudomonas aeruginosa* *Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant strains)	Enterobacteriaceae *P. aeruginosa* *Enterococcus* sp.	Enterobacteri *P. aeruginosa* *Streptococcus pneumoniae*, *aureus* (methi sensitive and methicillin-resistant) Mixe flora from aspiration
S. aureus	*Enterococcus* sp. (vancomy-cin-sensitive and vancomycin-resistant strains)		*Nocardia* sp.
Mixed infection	Rare: anaerobes (*Bacteroides* sp.) *Rhodococcus* sp.		*Mycobacteriur tuberculosis*, atypical *Mycobacteriur* *Rhodococcus* s (rare)

TABLE 11.6 Commonly Encountered Nonbacterial Pathogens in Renal Recipients Listed by Site of Infection

Sinopulmonary	Genitourinary Tract	Gastrointestinal System	Central Nervous System	Derm
Aspergillus, Candida, Cryptococcus	*Candida, Aspergillus (rare)*	Candida, Aspergillus (rare)	*Cryptococcus, Aspergillus,*	*Cand* derm (*Micr Trich Epide Mala*
Less common: Zygomycoses, *Coccidioides, Histoplasma, Pseudallescheria (Scedosporium)*			Less common: *Coccidioides, Pseudallescheria*	Less c *Crypt Asper Cocci Histo* phae
Pneumocystis	CMV, adenovirus, polyoma virus, papillomavirus	*Candida, Aspergillus,* Zygomycetes	CMV, HHV, VZV, West Nile virus, (rare: EBV, polyomavirus)	HHV,
CMV, HHV, respiratory viruses				
Less common: EBV				

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpes virus; VZV, varic virus.

Infections in kidney transplant recipients can be difficult to diagnose because concomitant immunosuppression and alterations in the immune response attenuate the usual clinical signs and symptoms of infection such as fever and leukocytosis. High clinical suspicion and prompt administration of empiric antimicrobial therapy are essential for effective treatment and prevention of infectious complications. Resistant infections or coinfection with more than one pathogen should be considered in an immunocompromised patient, especially when failing to respond to targeted antimicrobial therapy.

Urinary Tract Infection

The risk for genitourinary infection is directly related to complications of the surgical procedure, such as the urine leaks, wound hematomas, and lymphoceles, that can result in bacterial superinfection and abscess formation. Genitourinary tract manipulation during transplantation, urinary catheters, anatomic abnormalities (e.g., ureterovesicular stenosis, ureteral stricture, vesicoureteric reflux), and neurogenic bladder also predispose to post-transplantation urinary tract infection (UTI). Early catheter removal decreased the incidence of UTI in renal allograft recipients. In addition, routine antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX), usually for 6 months after transplantation, has substantially reduced the incidence of UTIs to less than 10% and virtually has eliminated secondary bacteremia unless urine flow is obstructed. Patients who are allergic to TMP-SMX can be treated with an oral quinolone.

A clean-catch midstream urine specimen should be submitted for quantitative bacterial and fungal culture. In renal transplant recipients, lower levels of bacteriuria may be associated with a significant risk for systemic infection. Infection may be more difficult to eradicate associated with ureteral stents that can lead to formation of biofilm. If possible, the stent should be removed and the tip sent for culture. Infected perigraft fluid collections or devitalized tissues often require percutaneous or open incision, in addition to directed antimicrobial therapy, to resolve the infection.

Bacteremia and Fungemia

Among renal transplant recipients, the urinary tract is the most common primary site of infection associated with secondary bacteremia. Among patients with bacteremia, poor

outcome is associated with gram-negative species, multidrug-resistant organisms, and *Candida* species, especially when the empiric antimicrobial therapy is inappropriate or delayed. Some studies suggest that bacterial sepsis increases the risk for CMV infection because of high levels of tumor necrosis factor-α (TNF-α) or dysregulated immune response to CMV in the context of serious bacterial infections.

For detection of bloodstream infection, two sets of blood cultures should be obtained before initiation of antimicrobial therapy. Fungemia is associated with high-dose corticosteroids for rejection; vascular, drainage, or urinary catheters; total parenteral nutrition; gastrointestinal inflammation or perforation; and diabetes mellitus. Fungal blood isolators may decrease the time to obtaining a positive blood culture result but are no more sensitive than routine bacterial blood cultures for detection of *Candida* species. If intravascular catheter-associated bacteremia is suspected, the device should be removed and the catheter tip should be cultured.

Pneumonia

Bacterial pneumonia is the most common life-threatening infection in kidney transplant recipients. The risk for pneumonia is increased among patients who require prolonged intubation, those with structural lung disease, and those with diminished gag reflex, prolonged nasogastric tube use, or impaired diaphragmatic function that increase the risk for aspiration. Hospital environmental exposure to certain species from contaminated water or aerosols, including *Legionella* and *Pseudomonas,* also increase the risk for pneumonia.

Diagnostic specimens for post-transplantation pneumonia may include blood, expectorated sputum, tracheal suction, bronchoalveolar lavage (BAL) fluid, transthoracic fine-needle aspirate, and, occasionally, lung biopsy. Blood cultures may assist in the etiologic diagnosis of pneumonia because 10% to 15% of patients with pneumonia have secondary bacteremia. Fiberoptic bronchoscopy with BAL and transbronchial biopsy is valuable in the diagnosis of severe pneumonia, especially when the episode is associated with an accessible pulmonary lesion. *Legionella* species can be cultured using charcoal media or detected using *Legionella-specific* nucleic acid probes or direct fluorescent antibody testing of respiratory specimens. In addition, *Legionella pneumophila* group 1 antigen can be detected in urine specimens. Respiratory specimens should be obtained for fungal culture and stain using a sensitive method such as calcofluor staining. Fluorescein-labeled monoclonal antibody staining of BAL or sputum specimens increases the sensitivity for detection of *Pneumocystis jiroveci*. *Nocardia* species can be identified presumptively when modified acid-fast staining reveals delicately branching filamentous and beaded gram-positive rods. Acid-fast staining of respiratory specimens, biopsy specimens, nodules, and lymph nodes may reveal mycobacterial forms. Once there is growth detected on culture, specific DNA probes for *M. tuberculosis* and *Mycobacterium avium* complex can confirm the diagnosis

of infections associated with these species.

Chest computed tomography (CT) is valuable in the diagnosis of infectious pneumonia and can be used to guide percutaneous or thoracoscopic biopsy of suspicious lesions. Concurrent immunosuppression and attenuated inflammatory response can modify the radiographic appearance and progression of pneumonia in transplant recipients. Noninfectious etiologies of pulmonary infiltrates are frequent in transplant recipients and include atelectasis, aspiration, contusion, hemorrhage, infarction or emboli, capillary leak, and pulmonary edema.

Intra-abdominal Infections

Preexisting medical conditions unrelated to end-stage renal disease, such as diverticulosis or biliary disease, can become apparent in the post-transplantation period. Immunosuppression, including corticosteroids, increases the risk for diverticulitis and colonic perforation and gastric perforation by diminishing mucosal immune surveillance, mucosal integrity, and fibroblastic activity. Hypoperfusion of the gastrointestinal mucosa, from hypotension or use of vasopressor agents, also increases the risk for mucosal perforation and secondary sepsis.

Surgical Site and Other Infections

The incidence of surgical site infection following kidney transplantation ranges from 2% to 25%. These infections typically occur within 3 weeks after transplantation and are usually related to technical complications and recipient factors, such as obesity and diabetes. The infection can involve the perinephric space or cause mycotic aneurysms at the site of the vascular anastomosis. Rarely, allograft nephrectomy is required. In pancreas-kidney transplant recipients, pancreatic abscess with gram-negative organisms or fungi may require surgical drainage or graft removal.

Diagnosis of infection associated with surgical wounds, skin nodules, or necrotic ulcers should include aspiration of any drainable material, a deep swab specimen from the site, and a biopsy specimen, when appropriate. Gram stain,

---

aerobic and anaerobic bacterial culture, and fungal and acid-fast stains and cultures should be performed. Percutaneous or open drainage may be necessary in case of infected perigraft collections, hematomas, or urinomas.

Culture of fluid collections should be performed in patients with unexplained fever or other signs and symptoms of infection in the early postoperative period. In most circumstances, percutaneous or open drainage of infected fluid collections or hematomas is necessary for resolving the infection. Ultrasound or CT guidance can assist in localization and drainage catheter placement. Patients with diarrhea, colitis, or abdominal symptoms who have received antibiotic therapy should have stool specimens collected for *Clostridium difficile* toxin A or B detection. Failure to remove

an infected device or drain the infected fluid collections may lead to prolonged antimicrobial therapy and an increased risk for resistance, treatment failure, drug toxicity, and graft dysfunction.

Approach to the Kidney Transplant Recipient with Fever

The differential diagnosis of fever in the kidney transplant recipient is broad and includes infection, graft rejection, drug allergy, and noninfectious systemic inflammatory response (e.g., pancreatitis, pulmonary embolism, or cytokine release syndrome from murine-monoclonal antibody preparations). Although fever may accompany acute rejection, most patients with rejection are afebrile. Temperature elevations may occur during treatment of rejection with both OKT3 and the polyclonal antibodies as a result of cytokine release (see Chapter 5).

MICROBIAL ETIOLOGY, TREATMENT PRINCIPLES, AND SPECIFIC THERAPY

Bacterial Infections

The bacterial pathogens in the early post-transplantation period are similar to those causing health care-associated infections in the nontransplant surgical population (Tables 11.5 and 11.6). In the early post-transplantation period, Enterobacteriaceae, and *Staphylococcus* and *Pseudomonas* species are the most commonly isolated health care pathogens and increasingly are multidrug resistant. Aerobic gram-negative bacilli constitute nearly half of all pathogens detected by blood culture, and infection is associated with a 2-week mortality rate of 11%. Secondary bacteremia most commonly arises from the urinary tract, lung, abdomen, or surgical wound. Although uncommon, infective endocarditis in the early post-transplantation period has been associated with *S. aureus,* coagulase-negative staphylococci, *Escherichia coli, Acinetobacter* species, *Enterococcus* species including VRE, *Pseudomonas* species, and *Candida* species. Most of these episodes are associated intravascular devices or surgical site infection.

Aerobic gram-negative bacilli, including Enterobacteriaceae and *P. aeruginosa, are* the most common organisms causing pneumonia and UTIs in kidney transplant recipients. Additional pathogens include *S. aureus* and enterococci (pneumonia and UTI), *S. pneumoniae, Legionella* species, and *Candida* species (UTI). Increasingly, *Klebsiella pneumoniae* and *E. coli* strains with resistance to extended-spectrum cephalosporins are associated with nosocomial urinary tract infections.

The most common bacterial organisms causing surgical site infection include *Staphylococcus* and *Streptococcus,* aerobic gram-negative bacteria, especially *E. coli, Enterobacter* species, and *Pseudomonas* species, and enterococci.

Vancomycin-Resistant Enterococcus

Rates of VRE colonization among solid organ transplant recipients range between 11% and 63%, and infection occurs in 1% to 16% of patients. Most VRE infections occur within the first month after transplantation and include

bacteremia, intra-abdominal and biliary tract, urinary tract, and surgical wounds. Risk factors for VRE infection include VRE colonization, prolonged hospitalization, and intensive care unit stays; broad-spectrum antibiotics; immunosuppression; renal insufficiency and hemodialysis; receiving a CMV-seropositive donor organ; prolonged operative time; and reoperation. It is uncertain whether VRE infection is an independent risk factor for death or simply a marker for debilitated, immunocompromised patient. A single, positive blood culture for VRE may represent a contaminant, especially if drawn from a central venous catheter but is more likely to be clinically significant when associated with a positive culture from a normally sterile site or infected wound. Multiple positive blood cultures indicate significant bacteremia and prompt directed therapy.

VRE colonization can be seen in open wounds, urine, and stool and should be interpreted accordingly. VRE colonization may persist for months to years in kidney transplant patients. Recommendations to decrease the risk for VRE colonization and infection include limiting the use of vancomycin and broad-spectrum antibiotics, especially those with anaerobic activity; active surveillance cultures to detect VRE stool colonization; use of contact precautions; and meticulous hand hygiene. VRE colonization may not be detected from a single stool or perirectal culture and three samples should be obtained at weekly intervals for at least 3 weeks before discontinuing isolation precautions.

Management of VRE should include removal of infected medical devices, drainage of fluid collections, and relieving urinary or biliary obstruction. Linezolid, quinupristin-dalfopristin (for *Enterococcus faecium* only), daptomycin, and tigecycline are active against VRE strains that are not susceptible to ampicillin and also can be used for treatment of susceptible enterococcal infections in a patient with a penicillin and vancomycin allergy. Linezolid can cause cytopenias, especially after more than 2 weeks of therapy, and requires close monitoring.

Clostridium difficile Infection

Diarrhea occurs in about 13% of kidney transplant recipients, most commonly within 2 weeks after transplantation and is most often associated with an infectious agent (41%) or medication (34%). Of infectious etiologies, *C. difficile* is the most common agent. *C. difficile-associated* syndromes include asymptomatic carriage, diarrhea, pseudomembranous colitis, intestinal perforation, and toxic megacolon. The later two complications are more common in infection associated with the hyper toxin producing epidemic strain of *C. difficile*. Most *C. difficile* infections are acquired nosocomially through either the hands of health care workers or from spore-contaminated

environmental surfaces. Risk factors include administration of broad-spectrum antianaerobic antimicrobial therapy; prolonged hospitalization; female gender; treatment for rejection with monoclonal antibodies; and intra-abdominal graft placement. *C. difficile* infection may result in fluid and electrolyte abnormalities and can lead to malabsorption of medications, including immunosuppressive agents. Oral metronidazole (500 mg 3 times daily) is the preferred first-line treatment for mild to moderate *C. difficile* infection. Oral vancomycin (125 to 250 mg 4 times daily) should be used for severe disease (e.g., occurring in the intensive care unit, in persons older than 60 years of age, or associated with hypoalbuminemia or white blood cell count > 15,000/mm^3) or if metronidazole fails. In patients with severe gastrointestinal dysmotility or ileus, oral agents may not reach the colonic mucosa and intravenous metronidazole should be administered along with oral vancomycin.

Listeriosis

In renal transplant recipients, infection with *L. monocytogenes* most commonly presents as meningoencephalitis or septicemia but also may cause febrile

---

gastroenteritis. Infection typically occurs 6 or more months after transplantation. Intravenous ampicillin (2 gm every 4 hours for 2 weeks.) should be used to treat bacteremia. Meningitis should be treated with high-dose ampicillin and gentamicin for 3 weeks. Repeat lumbar puncture should be performed to document cure. Many sporadic cases of listeriosis are associated with ingestion of processed meats. Patients should be instructed to eat only properly cooked meats and pasteurized dairy products.

Nocardiosis

The frequency of nocardia infections varies between 0.7% and 3% in solid organ transplant recipients. Although the prophylactic use of TMP-SMX has decreased the incidence of nocardia infection, *Nocardia* species should be considered in the differential diagnosis of infection occurring in the setting of early rejection, enhanced immunosuppression, neutropenia, and uremia. There are at least 12 species within the genus of *Nocardia*, with *N. asteroids* complex, *N. brasiliensis, N. otitidiscaviarum*, and *N. transvalensis* most commonly associated with infection among transplant recipients. Nocardia infection most commonly presents 1 to 6 months after transplantation with acute or subacute pneumonia, but hematogenous spread to the brain, skin and subcutaneous tissues, bone, and eye has been reported. After pulmonary disease is established, dissemination to the brain is common, and cerebral CT or magnetic resonance imaging (MRI) of the brain should be performed. High-dose TMP-SMX (15 mg/kg of trimethoprim in two to four divided doses, depending on the severity of illness) is the treatment of choice for most *Nocardia* species infections. However, resistance has been reported, and antimicrobial susceptibility testing is recommended. Other agents, including imipenem, amikacin, second- and third-generation cephalosporins, minocycline, and quinolones, may be used with TMP-SMX or in

combination in place of TMP-SMX when treating serious nocardia infection. Amikacin should be used with caution in the renal transplant patient because of the risk for nephrotoxicity. Surgical débridement and drainage may be required to manage brain abscesses or empyema. Because of the substantial risk for relapse in the setting of ongoing immunosuppression, treatment should be for at least 12 months and radiographic monitoring of the sites of infection should be performed at regular intervals. Following treatment, secondary prophylaxis with TMP-SMX should be considered.

Legionellosis

Legionella species infections have been reported in kidney transplant recipients. Risk factors include repeated corticosteroid boluses, prolonged mechanical ventilation, and exposure to Legionella-contaminated hospital water supplies. *L. micdadei* and *L. pneumophila* commonly cause pneumonia, but extrapulmonary involvement, including culture-negative endocarditis and renal, hepatic, and central nervous system infection, have been reported. Signs and symptoms of *L. pneumophila* infection include a nonproductive cough, a temperature-pulse dissociation, elevated hepatic enzymes, diarrhea, hyponatremia, myalgias, and altered mental status. Radiographic findings include alveolar or interstitial infiltrates, cavities, pleural effusions, or lobar consolidation. Diagnosis can be confirmed by culture on special media or direct-fluorescent antibody testing of sputum, tissue, or bronchoalveolar fluid. In addition, a urinary antigen test should be performed; this test has a reported 70% sensitivity and 100% specificity for *L. pneumophila* serogroup 1. Delayed treatment is associated with increased mortality, and empiric treatment should be administered in suspected cases. Macrolides, quinolones, tetracyclines, rifampin, and TMP-SMX have *in vitro* activity against *Legionella* species. In organ transplants, optimal treatment should include azithromycin and a quinolone. Erythromycin will increase and rifampin will decrease blood levels of the calcineurin inhibitors and should be avoided, if possible (see Chapter 5). Duration of treatment ranges from 14 to 21 days, depending on severity of illness.

Rhodococcus

Rhodococcus equi is an aerobic gram-positive coccobacillus that can cause infection in animals and in immunocompromised hosts, including renal transplant recipients. *Rhodococcus* most commonly causes pulmonary infection months to years after transplantation. Presentations include nodular or cavitary necrotizing pneumonia and empyema that may be confused with pulmonary tuberculosis. Aspiration of pulmonary nodules may reveal granulomatous inflammation with foamy macrophages with intracellular coccobacilli. Other clinical syndromes include sepsis, osteomyelitis, skin nodules, pericarditis, and lymphadenitis. Effective agents include quinolones, vancomycin, carbapenems, doxycycline, erythromycin, and TMP-SMX; β-lactams may be

ineffective. Recurrences can occur, and surgical drainage may be required.

Mycobacterial Infection

Tuberculosis (TB) and nontuberculous mycobacteria (NTM) are potential causes of serious infection in renal allograft recipients that may present as early as the first post-transplantation month. The incidence of active tuberculosis is estimated to be 1% to 4% following renal transplantation and is higher in those who resided in or traveled to a country with a high prevalence of TB infection. Radiographic presentations of pulmonary infection with *M. tuberculosis* and NTM include multilobar disease, focal infiltrates and nodules, empyema, pleuritis, or a combination of findings.

In the transplant population, atypical presentations of *M. tuberculosis* and NTM disease may delay diagnosis and contribute to morbidity. Special vigilance for reactivation tuberculosis is warranted, especially among transplant recipients with a prior history of mycobacterial infection, with old granulomatous disease on chest radiograph, or from countries with high TB prevalence. Up to 40% of renal transplant recipients with reactivation tuberculosis will present with disseminated infection, with involvement of the skin, skeleton (bone and joint), or central nervous system. Finding granuloma in biopsy specimens from extrapulmonary sites should suggest disseminated disease. Because of the increase in multidrug-resistant (MDR) strains, appropriate therapy should include four agents: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) or intramuscular streptomycin (SM) for 2 months or until susceptibility tests results are available followed by up to 10 months of INH and RIF. Adverse effects associated with antituberculous agents include hepatitis (INH > PZA > RIF), peripheral neuritis and optic neuropathy (INH, EMB), hearing loss and azotemia (SM), gastrointestinal intolerance (INH, RIF, EMB, PZA), and neutropenia (RIF > ETH). Both INH and RIF affect the cytochrome P-450 enzyme system. INH increases cyclosporine and tacrolimus levels, and RIF decreases these drug levels, increasing the risk for rejection. These interactions are usually predictable and may occur within 1 to 3 days of initiating antituberculous therapy. Appropriate dosage adjustments and monitoring are required.

Infection with NTM, including *M. kansasii, M. fortuitum, M. chelonei, M. xenopi, M. marinum, M. haemophilum,* and *M. abscessus,* has been reported in renal transplant recipients. These pathogens can be cultured from sputum, lung tissue, skin, bone, and other disseminated sites. Many of the NTM are intrinsically resistant to standard antituberculous agents, and susceptibility testing should be performed against standard tuberculous agents, quinolones,

---

macrolides, cephalosporins, and linezolid. Treatment typically includes combinations of agents for prolonged durations (e.g., longer than 12 months). Patients with osteomyelitis and extensive soft tissue disease may require surgical intervention. *M. fortuitum* may cause bloodstream infection associated with intravascular devices and

prompt device removal is critical.

Mixed Infections

Concurrent bacterial, fungal, and viral infections most often occur in the setting of repeated episodes of rejection and resultant enhanced; postoperative health care-associated infections (e.g., pneumonia or intra-abdominal abscess); or immunomodulation from CMV or other virus infection, particularly respiratory viruses and hepatitis C. The presence of CMV in bronchoalveolar specimens or blood should always be investigated in fungal pulmonary infections.

ANTIMICROBIAL THERAPY

Antimicrobial therapy is given for the following indications:

- *Prophylaxis*: Antimicrobial agents are used to prevent a commonly encountered infection in the immediate postoperative period (e.g., surgical prophylaxis).
- *Empiric therapy*: Antimicrobials are administered without identification of the infecting pathogen.
- *Specific therapy*: Antimicrobials are administered to treat an infection with a diagnosed pathogen.

Surgical Prophylaxis

Preoperative antimicrobial prophylaxis reduces the frequency of surgical site infection. The agent should have activity against skin pathogens (e.g., staphylococci, streptococci) and urinary tract pathogens *(E. coli* and *Klebsiella* and *Proteus* species). Cefazolin (1 to 2 g based on body weight) generally is preferred and should be administered within 1 hour of the surgical incision. The choice of antimicrobial agent for renal transplant prophylaxis should also be based on institution-specific antimicrobial susceptibility patterns and a careful review and history of drug allergies. Surgical prophylaxis should given as a single dose or discontinued after no more than 24 hours to minimize the risk for toxicity and superinfection, and limit cost.

Empiric and Directed Antibacterial Therapy

For patients with suspected bacterial infection, the choice of empiric therapy should be guided by the following considerations: potential sites of infection; prior culture and susceptibility results; recent antimicrobial exposure; time since transplantation; the severity of renal and hepatic dysfunction; and the net state of immunosuppression. Initial empiric therapy should include one or more broad-spectrum antibacterial agents. Commonly used agents for empiric therapy include third-generation cephalosporins, β-

lactam and ß-lactamase inhibitor combinations, carbapenems, fluoroquinolones, or vancomycin, if line-associated infection is suspected. When *P. aeruginosa* is suspected or documented, combination therapy with an antipseudomonal penicillin (i.e., piperacillin), carbapenem, ceftazidime, or cefepime, plus an aminoglycoside or antipseudomonal fluoroquinolone (i.e., ciprofloxacin, levofloxacin) is recommended for synergistic bactericidal activity and potentially to limit the emergence of resistance. Aminoglycosides, although generally active against gram-negative bacteria, should be used with caution in renal allograft recipients because of the increased risk for nephrotoxicity. When the culture and sensitivity results are available, therapy

should be modified to treat the infection with a narrow-spectrum agent to limit the risk for superinfection with multidrug-resistant organisms, toxicity, and cost. Potential interactions between antimicrobials and immunosuppressive agents are discussed in Chapter 5.

FUNGAL INFECTIONS

Despite ongoing refinements in immunosuppressive therapy, graft preservation, and surgical techniques, fungal infections remain a significant cause of morbidity and mortality in renal transplant recipients (Table 11.7). Although the incidence of fungal infections in renal transplant recipients is less than that reported for other solid organ transplant recipients, the mortality from fungal infections remains high and is related to the pathogenicity of the organisms, site of infection, impaired host inflammatory response, limited diagnostic tools, potential for rapid clinical progression, failure to recognize a high-risk patient, and comorbidities, such as renal failure and diabetes mellitus.

Colonization with yeasts and molds occurs frequently in transplant candidates with end-stage renal disease and after transplantation because of exposure to broad-spectrum antibacterial agents, domiciliary and hospital exposures, immunosuppressive therapy, especially corticosteroids, and the presence of urinary catheters and endotracheal tubes. Isolation of *Candida* species from cultures of stool, respiratory, and urine samples occurs commonly in kidney transplant recipients receiving corticosteroids and broad-spectrum antimicrobials and does not necessarily imply infection. However, repeatedly positive fungal cultures from a single or from multiple sites may herald invasive candidiasis in the appropriate clinical setting.

Candida species, *Aspergillus* species, *P. jiroveci,* and *C. neoformans are* the most common fungal pathogens reported in renal transplant recipient. Zygomycetes *(Mucor, Rhizopus* species), hyalohyphomycoses, phaeohyphomycosis, and the geographically restricted mycoses (*Histoplasma, Coccidioides, Blastomyces* species) are more commonly encountered under special clinical circumstances, such as immunomodulating viral infection, chronic graft dysfunction, or treatment of post-transplantation malignancies.

Donor-transmitted fungal infection is uncommon among kidney transplant recipients, but cases of *Candida*, *Aspergillus*, *Histoplasma*, *Coccidioides*, *Cryptococcus*, and *Scedosporium* species have been reported, usually associated with unrecognized infection within the donor allograft or in the blood compartment. All donors should be evaluated for evidence of active or occult fungal infection, particularly in the blood and urine.

Candida infections occur most commonly during the first month following transplantation and are usually associated with transplant surgical technical complications, early rejection, and enhanced immunosuppression. *Candida* infection is most commonly associated with an endogenous source of colonization, but inadequate health care worker hand hygiene may contribute to acquisition from an exogenous source. *C. albicans* is the most common species, followed by *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*. Speciation is clinically useful because nonalbicans *Candida* species vary in *in vitro* susceptibility to amphotericin B and azoles. Sites of *Candida* infection include mucocutaneous candidiasis and esophagitis; wound infections; cystitis, pyelonephritis, and ureteral obstruction by Candida elements or “fungal ball”; intra-abdominal infections, including infected perigraft fluid collections or peritonitis; and intravascular device-associated fungemia. Renal parenchymal infection most often results from candidemia and hematogenous spread, although ascending infection from the bladder can occur. Candiduria is typically asymptomatic but may be associated with cystitis or upper tract infection. Patients with genitourinary tract stents and recurrent funguria often require removal of foreign body to eradicate the infection.

TABLE 11.7 Incidence and Distribution of Invasive Fungal Infections (

Proportion of IFI (%)

Organ Transplant	Incidence of IFI (%)	*Aspergillus*	*Candida*	*Cryptococcus*	Other Fungi	*A*
Renal	0-20	0-26	76-95	0-39	0-39	2

Pancreas and pancreas-kidney	6-38	0-3	97-100	—	—	1

Data derived from several series using varying definitions of fungal infection betwee

The risk for fungal infection after simultaneous pancreas-kidney (SPK) and pancreas after kidney (PAK) transplantations is similar to liver transplant recipients. More that 45% of these infections are caused by *Candida* species. Risk factors include older donor or recipient age, bladder versus enteric drainage (SPK recipients), retransplantation versus primary transplantation (PAK recipients), and vascular graft thrombosis. Bladder drainage of pancreatic secretions and longer duration of urinary catheterization favors urinary tract colonization with *Candida* species and early postoperative fungal UTIs. Fungal infection of the pancreatic allograft is associated a high risk for graft loss and mortality rates as high as 20%.

The period of 1 to 6 months after kidney transplantation is marked by opportunistic, relapsed, and residual fungal infection. *Cryptococcus,* endemic mycoses, hyalohyphomycosis, phaeohyphomycosis, zygomycosis, and dermatophytes most commonly occur 6 or more months after transplantation. Conditions that intensify the net state of immunosuppression may shift the timeline for fungal infection forward. Cryptococcus often presents as meningitis but may cause space-occupying brain lesions; pulmonary, dermatologic, skeletal, organ-specific disease; aspergillosis—pneumonia and other tissue-invasive forms, including genitourinary, central nervous system, rhinocerebral, gastrointestinal, skin, wound, and musculoskeletal disease; zygomycosis with *Rhizopus* and *Mucor* species—pulmonary, rhinocerebral, cutaneous disease; coccidioidomycosis—pneumonia, meningitis, musculoskeletal, and skin involvement; histoplasmosis—pneumonia, mediastinitis, skin, and disseminated disease; *Penicillium marneffei*—pneumonia; and scedosporiosis—pneumonia and disseminated disease.

Patients at risk for aspergillosis include those receiving repeated courses of enhanced immunosuppression for rejection and those with chronic graft dysfunction, diabetes, comorbid medical illnesses, or CMV infection. Diagnosis of aspergillus infection depends on a high clinical suspicion, isolation of *Aspergillus* species from a sterile body site or repeated isolation from the respiratory tract, and typical radiographic findings. Radiologic appearances of pulmonary aspergillosis in kidney transplant recipients include nodules, diffuse or wedgeshaped opacities, empyema, or cavitary forms. Serial measurement of aspergillus galactomannan in the serum may aid in the early diagnosis

of invasive aspergillosis in the high-risk setting.

Prophylaxis

During induction or periods of enhanced immunosuppression, oral, nonabsorbable, or topical antifungal agents, such as clotrimazole or nystatin, typically are administered to prevent mucocutaneous *Candida* infection. Although prophylaxis with a systemic antifungal agent is not recommended after uncomplicated renal transplantation, it may be indicated in those with persistent candiduria. In such cases, an azole, echinocandin, or a lipid-based formulation of amphotericin B can be administered for a duration proportional to the risk for fungal infection. Renal transplant recipients with a history of prior treatment of an endemic mycosis or radiographic evidence of old, "healed" granulomatous disease associated with coccidioidomycosis or histoplasmosis benefit from long-term (lifelong) prophylaxis with an appropriate azole.

Treatment

Historically, invasive candidiasis, cryptococcosis, coccidioidomycosis, histoplasmosis, and aspergillosis were treated with amphotericin B deoxycholate (AmB).

Because of inherent toxicities and intolerance, newer agents have increasingly been used in renal transplant recipients. The lipid formulations of amphotericin B are all associated with lower risks for nephrotoxicity, metabolic derangements, and infusion-associated side effects than is AmB. Higher therapeutic dosages can be administered, and broad-spectrum antifungal activity is generally maintained.

Voriconazole appears to be superior to conventional AmB for the treatment of invasive aspergillosis and also has *in vitro* activity against a wider range of organisms. Available in both intravenous and oral formulations, the drug is generally well tolerated, but some patients experience visual hallucinations or severe photosensitivity. Oral posaconazole has excellent activity *in vitro* against *Candida, Aspergillus,* and *Mucor* species, but experience in solid organ transplant recipients is limited to date. Although itraconazole has good *in vitro* activity against *Aspergillus* species, its use is generally reserved for treatment of less-severe aspergillosis or maintenance therapy following initial response to lipid amphotericin or voriconazole and for treatment of endemic mycoses. Fluconazole is the first-line agent of the treatment or prevention of reactivation coccidioidomycosis in renal transplant recipients. The long-term use of fluconazole may be associated with the development of fungal resistance or tolerance, as well as with the risk for fungal superinfection with *C. glabrata, C. krusei,* or *C. tropicalis.* Fluconazole and 5-flucytosine can be used for cryptococcal disease. All of the azoles impair calcineurin inhibitor metabolism and increase calcineurin blood levels (see Chapter 5). This effect is most consistent with ketoconazole, and its use may permit a reduction in cyclosporine or tacrolimus dose of up to 80%.

The echinocandins, including caspofungin, anidulafungin, and micafungin, inhibit

synthesis of fungal cell wall protein β_{1-3} glucan and are fungicidal for *Candida* species, including fluconazole-resistant species. Available only as intravenous formulations, the echinocandins are effective, well tolerated, and have few drug-drug interactions. As a result, they increasingly are being used to treat serious infections associated with nonalbicans *Candida* species in transplant recipients. Coadministration of caspofungin with tacrolimus results in modest (about 20%) reduction in tacrolimus levels and an increased incidence of abnormal liver function tests with cyclosporine.

The development of any serious fungal infection in a transplant recipient mandates a critical evaluation of the immunosuppressive regimen. The corticosteroid dose should be minimized, the blood levels of cyclosporine and tacrolimus should be kept in the low therapeutic range, and other immunosuppressive agents often can be discontinued temporarily. Clinical treatment failure for life-threatening fungal infection despite appropriate antifungal therapy may warrant discontinuation of immunosuppression at the cost of graft loss.

Pneumocystosis

P. jiroveci (formerly *carinii)* pneumonia most often occurs 2 to 6 months after transplantation (median time, 4 months). It typically presents with fever, nonproductive cough, arterial-alveolar mismatching, and diffuse interstitial infiltration or focal air space consolidation on chest radiograph. Unusual presentations are possible in renal transplant recipients, including pulmonary mass lesions. BAL with transbronchial biopsy and staining is a highly sensitive method of identifying pulmonary disease. First-line treatment is with TMP-SMX 15 mg/kg for 21 days. Treatment of severe disease should include adjunctive steroids as for HIV-infected persons with PCP (60 mg/day initially, then taper). Second-line agents include intravenous pentamidine (4 mg/kg per day), dapsone-trimethoprim (100 mg dapsone daily with trimethoprim 100 mg twice daily), or clindamycin plus primaquine (600 mg 4 times daily clindamycin with 30 mg base daily primaquine). Adverse effects of trimethoprim include nephrotoxicity, pancreatitis, and bone marrow suppression. Dapsone is associated with hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency. Mild to moderate *P. jiroveci* pneumonia can be treated with atovaquone (750 mg orally twice daily for 21 days) in patients allergic to TMP-SMX. Prophylactic agents, in order of efficacy, include TMP-SMX (single-strength tablet 3 times weekly), monthly intravenous or aerosolized pentamidine, daily dapsone, and daily atovaquone. Prophylaxis against disease should be reinstituted following augmentation of immunosuppression, such as steroid bolus for acute rejection.

VIRAL INFECTIONS

Viral infections are a major problem in allograft recipients, most commonly 1 to 6 months after transplantation. Clinical disease can occur later, especially after

intensification of immunosuppression or physiologic insults that increase the net state of immunosuppression. EBV-related lymphoproliferative disorder is discussed in Chapter 10.

Cytomegalovirus

CMV infection occurs primarily after the first month of transplantation with an estimated incidence of 30% to 78% if antiviral prophylaxis is not administered, depending on the serologic status of the donor and recipient (Table 11.3). CMV can be transmitted by the allograft, through blood products, or by sexual contact and establishes lifelong latency after primary infection. Among all organ transplants, renal transplant recipients have the lowest risk for CMV disease in the absence of antiviral prophylaxis, whereas pancreas and kidney-pancreas transplant recipients are at substantially higher risk. In general, the dose, duration, agents, and intensity of immunosuppression determine the risk for CMV among transplant recipients. Specific risk factors include CMV donor-recipient mismatching and the use of lymphocyte-depleting preparations induction for rejection therapy (see Chapter 5). Other risk factors include comorbid illnesses, neutropenia, and, potentially, coinfection with HHV-6 and -7.

Active CMV infection may be symptomatic or asymptomatic and is characterized by viral replication and shedding with a specific host cellular immune response to CMV. Primary CMV infection represents infection in the previously uninfected seronegative host, whereas secondary CMV infection represents infection in a previously infected seropositive host caused by either reactivation of latent endogenous virus, or suprainfection with new virus strain. CMV disease refers to symptomatic acute CMV infection and includes CMV syndrome (fever, fatigue, leukopenia or thrombocytopenia, and detectable CMV viremia) and invasive CMV disease (e.g., pneumonitis, hepatitis, or gastrointestinal involvement such as colitis or enteritis, or involvement of the allograft itself).

CMV disease is associated with immune modulation and dysregulation, especially of helper T cells, and can culminate in opportunistic infection, allograft injury or rejection, and the development of PTLD. Host mediators implicated in reactivation of CMV include TNF, catecholamines, and proinflammatory prostaglandins. TNF binds to the TNF receptor of cells latently infected with CMV and generates nuclear transcription factors protein kinase C and nuclear factor-KB (NF-κB), which act as promoters of the immediate-early gene of CMV initiating replication. CMV infection induces anti-endothelial cell antibodies that contribute to both acute and chronic rejection.

CMV disease most commonly presents as a viremic syndrome, manifest by fever, malaise, leukopenia, and transaminitis. Pneumonitis is the most serious manifestation of CMV disease and is characterized by dyspnea, hypoxemia,

interstitial infiltrates, and the detection of CMV antigens, nucleic acids, or inclusion bodies on BAL. CMV upper and lower gastrointestinal disease includes esophagitis, cholecystitis, duodenitis, hepatitis, and colitis. Diagnostic endoscopy can reveal solitary or multiple mucosal ulcerations with hemorrhage. Tissue specimens should be stained for CMV using immunofluorescent anti-CMV antibody and examined for inclusion bodies. CMV retinitis is uncommon in transplant recipients and can be diagnosed by direct funduscopy. Central nervous system CMV disease (e.g., meningitis, encephalitis, myelitis) may be more difficult to diagnose. Neurologic disease caused by other neurotropic opportunistic pathogens, and drug toxicities, should be simultaneously investigated. Multiorgan involvement can be observed in disseminated CMV disease.

Diagnosis

Historically, tissue-invasive CMV disease was diagnosed by histopathology, but this approach can be associated with diagnostic delays or inadequate specimen collection. Detection of serum CMV IgM or IgG antibody by EIA is useful for pretransplantation screening and for documenting seroconversion but is insensitive for the diagnosis of CMV disease. Culture-based methods include conventional tissue culture and shell vial centrifugation and can be performed on blood, buffy coat blood fraction, urine, cerebrospinal fluid (CSF), respiratory secretions, or other tissue specimens. Tissue culture is most commonly employed for antiviral resistance testing, although PCR-based methods are available that do not require isolation of virus from culture. Staining conventional cell culture or shell vial culture with monoclonal antibody against early CMV viral antigens at 48 hours can decrease the time to diagnosis but is not as sensitive as traditional viral culture. Detection of CMV pp65 antigen in peripheral blood lymphocytes by a semiquantitative fluorescent assay also is more rapid than traditional culture methods. Quantitative detection CMV DNA from blood or CSF using PCR or DNA hybridization is commonly used to diagnose CMV disease associated with viremia and to monitor response to antiviral therapy. Qualitative CMV DNA detection by PCR is extremely sensitive but cannot differentiate active disease or latent infection.

Treatment

Effective antiviral agents for CMV prophylaxis and treatment have substantially decreased the morbidity and mortality associated with CMV disease. Oral valganciclovir (900 mg twice daily) has been demonstrated to have comparable safety and efficacy to intravenous ganciclovir for clearing CMV viremia and resolving clinical disease in solid organ transplant patients with mild to moderate CMV disease. Patients with high CMV viral loads (e.g., $>5 \times 10^5$ copies/mL) or severe tissue invasive disease, and those who fail to achieve a reduction in viral load after 7 or more days of oral valganciclovir treatment should be treated with intravenous ganciclovir (5 mg/kg every 12 hours). Patients with CMV disease should receive at least weekly monitoring of blood viral load, and antiviral therapy should be continued until there is suppression of viremia, typically 14 to 21 days. Renal transplant recipients with ongoing risk factors for CMV

should receive long-term maintenance therapy with oral ganciclovir (1000 mg 3 times daily), valganciclovir (450 to 900 mg once daily) or valacyclovir (2 g, 4 times daily). Adverse effects of ganciclovir include reversible, doserelated granulocytopenia and thrombocytopenia, fever, rash, seizures, nausea, myalgias, abnormalities in liver enzyme determinations, and, rarely, pancreatitis. Drug interactions include an increased seizure risk when used in combination with imipenem, and additive marrow suppression with azathioprine, mycophenolate, and TMP-SMX.

Anecdotal experience in treating refractory CMV disease suggests that the addition of CMV hyperimmune globulin (CMVIG) or pooled intravenous immune globulin (IVIG) to ganciclovir may improve the clinical response. Cidofovir and foscarnet can be used to treat disease associated with ganciclovirresistant CMV strains. However, the risk for additive nephrotoxicity with calcineurin blockers has limited their use.

Prevention

Regimens to limit the risk for CMV disease and to improve patient and allograft survival vary from center to center and are based on the CMV serostatus of the donor and recipient and an assessment of the net state of immunosuppression. In practice, two strategies are used for CMV prevention: universal prophylaxis and preemptive therapy. Universal prophylaxis involves administering antiviral therapy to all at-risk patients immediately after transplantation for a defined duration dependent on the perceived duration of risk and net state of immunosuppression. Preemptive or targeted therapy involves monitoring patients at regular intervals for early evidence of CMV replication by use of a laboratory assay such as CMV quantitative PCR. Patients with laboratory evidence of early CMV replication are treated with antiviral therapy to prevent symptomatic disease. The approach of universal prophylaxis may be more useful for patients at high risk for CMV disease, whereas preemptive therapy may be more useful for patients at low or intermediate risk for CMV disease.

Antiviral agents currently used for universal prophylaxis include intravenous or oral ganciclovir, oral valganciclovir, valacyclovir, CMVIG, and a combination of antiviral therapy and CMVIG. Compared with the intravenous formulation, oral ganciclovir is substantially less bioavailable (4% to 6%) and achieves significantly lower serum levels, but it is more convenient to administer. Valganciclovir, the L-valine ester of ganciclovir, is administered in a dose of 450 to 900 mg per day by mouth for CMV prophylaxis and produces similar area under the curve values to intravenous ganciclovir (5 mg/kg per day) and much higher values than oral ganciclovir (3 g per day). In a large, randomized clinical trial, once-daily valganciclovir was similarly safe and effective as oral ganciclovir administered 3 times daily for 100 days for the prevention of CMV disease in high-risk D+/R- solid organ transplant recipients. In a subanalysis, valganciclovir was more effective than ganciclovir in preventing CMV disease at 6 months among kidney transplant recipients. In nonblinded, nonrandomized trials,

CMVIG reduced the incidence of virologically confirmed CMV-associated syndromes and secondary opportunistic infections in D+/R- renal transplants. However, a recent systematic review failed to demonstrate a benefit of CMVIG administered prophylactically.

CMV-positive transplant patients who are treated with antilymphocytic agents, or who require multiple treatments for rejection, have a high incidence of symptomatic CMV disease. Although controlled trials are lacking, intravenous ganciclovir (2.5 to 5 mg/kg per day) or valganciclovir (450 to 900 mg once daily) administered during antilymphocyte antibody treatment or intensified immunosuppression courses followed by a period of oral ganciclovir or valganciclovir may reduce this risk. Ganciclovir, valganciclovir, and valacyclovir require dosage adjustment for decreased creatinine clearance.

Herpes Simplex Virus and Varicella-Zoster Virus

HSV infection typically develops within the first 6 weeks after transplantation and most commonly involves mucosal surfaces. Infection occasionally can disseminate to visceral organs and cause esophagitis, hepatitis, and pneumonitis. Most infections are caused by reactivation of endogenous latent virus, although primary infection transmitted from the allografts has been described. Both

acyclovir and ganciclovir are active against herpesviruses *in vitro*, and both are useful in the treatment or prophylaxis of HSV. Alternative agents include valacyclovir and famciclovir. Acyclovir can be given intravenously or orally for mucocutaneous infections. For treatment of HSV encephalitis, a higher dosage is given by slow infusion to prevent crystallization within the renal tubules.

Herpes zoster ("shingles") develops in about 10% of adult renal transplant recipients and may involve two or three adjoining dermatomes. Infection is usually caused by reactivation of latent disease. Unless there are contraindications, VZV-seronegative transplant candidates should receive two doses of live varicella vaccine, and seropositive candidates 60 years or older should receive a single dose of live zoster vaccine to decrease the risk for varicella disease following kidney transplantation.

Acyclovir, famciclovir, and valacyclovir can be used for treatment of herpes zoster and primary varicella infection. Primary varicella and rarely disseminated zoster can cause pneumonia, encephalitis, disseminated intravascular coagulation, and graft dysfunction. Intravenous acyclovir (10 to 15 mg/kg every 8 hours as a slow infusion) should be given for the treatment of primary varicella and disseminated zoster. Oral acyclovir, valacyclovir, famciclovir, or ganciclovir may be appropriate for treatment of mild dermatomal zoster. Following exposure to a person with primary varicella or zoster, transplant recipients who are susceptible or nonimmune to VZV should be given VZV immune globulin as soon as possible for maximal effectiveness but no later than 96 hours after exposure.

Other Human Herpesviruses

HHV-6, -7, and -8 may reactivate following renal transplantation. Although more than 90% of adults are seropositive for HHV-6 and 7, only 0% to 5% are seropositive for HHV-8. Neither serology nor PCR of peripheral blood lymphocytes can reliably distinguish active from latent infection with these viruses, and routine monitoring or treatment of asymptomatic individuals is not recommended. HHV-6 reactivates in 31% to 55% of organ transplant recipients, most commonly occurring during episodes of acute rejection, associated with calcineurin inhibitor toxicity, and during the first 4 weeks after transplantation. Reactivation of HHV-6 is associated with CMV disease and an increased risk for invasive fungal infection and can cause hepatitis, pneumonitis, and encephalitis. Symptomatic HHV-6 infection should be treated with ganciclovir and reduction of immunosuppression. HHV-8 seroconversion occurs in up to 12% of seronegative kidney transplants, usually within 3 months of transplantation, and can be primary or transmitted from the donor kidney. HHV-8 infection is associated with Kaposi sarcoma that occurs a median of 30 months after transplantation. Diagnosis is supported by pathology and by the presence of HHV-8 DNA sequences in involved tissue. Treatment consists of radiation and chemotherapy. The clinical significance of primary or reactivation HHV-7 infection is poorly characterized.

Adenovirus

Adenovirus can cause hemorrhagic cystitis, fever, renal dysfunction, and, rarely, dissemination with pneumonia, hepatitis, and death. After transplantation, infection may result from reactivation of latent adenovirus or primary infection from an exogenous source or from the renal allograft. Disseminated disease is more common after primary infection. Definite diagnosis is by kidney biopsy that typically reveals granulomatous interstitial nephritis, tubular necrosis, and ground-glass-like intranuclear viral inclusion bodies in tubular cells. Intravenous ribavirin, either alone or in combination with IVIG, has been used with some success and reduction in immunosuppression may be of benefit.

BK Virus

Polyomaviruses associated with human disease include BK virus and JC virus. BK virus causes latent infection of the kidney; with reactivation during immune suppression, it may cause tubulointerstitial nephritis and ureteral stenosis or stricture. The peak incidence of primary BK infection occurs in children 2 to 5 years of age, and 60% to 80% of adults are seropositive. Rates of infection in renal transplant recipients' range between 10% and 60%, with a bimodal distribution of disease between 10 days and 6 weeks after transplantation for primary infection and 5 weeks and 17 months for reinfection or reactivation. Risk factors for infection and disease include donor seropositivity, degree of immune suppression, use of tacrolimus and mycophenolate

mofetil, and allograft rejection. Definitive diagnosis requires a renal biopsy. Monitoring for BK virus in the plasma by DNA PCR is more specific for diagnosis of BK nephropathy than is detection with urine specimens. However, the detection of BK virus DNA in urine specimens may provide the first evidence of polyomavirus infection in the patient. Management involves reduction of immunosuppression with close monitoring for rejection. Leflunomide, cidofovir, IVIG, and corticosteroids may be of clinical benefit. Leflunomide is the drug of first choice because of its combined antiviral and immunosuppressive properties and its lack of nephrotoxicity (see Chapter 5). A maintenance dose of 20 to 40 mg daily is usually adequate.

Influenza Types A and B, Parainfluenza Virus, and Respiratory Syncytial Virus

Community respiratory viruses may cause significant morbidity and mortality in renal transplant recipients. These seasonal viruses can be transmitted by virus-laden respiratory droplets and aerosols by direct person-to-person contact or by contact with contaminated environmental surfaces. Renal transplant recipients may be the "sentinel" cases for a community influenza outbreak. Community respiratory virus disease usually presents with upper respiratory tract symptoms and high fever, myalgias, arthralgias, anorexia, and mucosal inflammation. Illness ranges from mild upper respiratory illness, to bronchiolitis, viral pneumonia with respiratory failure, and suprainfection with fungal or bacterial pathogens, such as S. *aureus, Streptococcus* species, and gram-negative bacilli. Simultaneous CMV reactivation may occur as a result of immunomodulation. Rapid detection of virus-infected upper respiratory cells (e.g., nasopharyngeal washing, respiratory secretions) using virus-specific fluorescent-labeled antibody probes can facilitate the diagnosis, appropriate isolation, and treatment of patients with viral respiratory infections.

All renal transplant recipients should receive annual immunization with inactivated influenza vaccine. The vaccine is safe and confers high seroprotection (range, 79% to 93%) similar to normal, healthy volunteers. Live, intranasal influenza vaccine should not be administered to renal transplant recipients or their household contacts.

The neuraminidase inhibitors oseltamivir and zanamivir are active against most influenza A and B and are effective if started within 36 to 48 hours after onset of symptoms. They result in a modest decrease in the duration of illness and significantly decrease the risk for secondary bacterial complications. Because of the high prevalence of resistant influenza A virus, amantadine and rimantadine should no longer be used for treatment or prophylaxis of influenza. During community or institutional outbreaks of influenza, susceptible persons should be vaccinated and antiviral prophylaxis administered for 2 weeks until antibodies develop.

RSV pneumonitis may respond to intravenous or aerosolized ribavirin delivered in a controlled contained administration system given over 24 hours. RSV monoclonal antibody (palivizumab) may be combined with aerosolized

ribavirin before respiratory failure develops, although their use has not been studied in renal transplant recipients. Parainfluenza virus (types 1 to 4) is a paramyxovirus; it can occur during fall and winter months, or sporadically. Disease spectrum in renal transplant recipients can mimic influenza and can include mild upper respiratory disease, pneumonia, and death. Diagnosis of parainfluenza includes viral isolation, shell vial assays, and rapid antigen detection kits on cultured material or direct clinical specimens. Treatment options are limited for parainfluenza infection, but zanamvir has in vitro activity against this paramyxovirus.

Parvovirus

In transplant recipients, parvovirus B19 infection is a cause of refractory severe anemia, pancytopenia, thrombotic microangiopathy, fibrosing cholestatic hepatitis, encephalitis, and graft dysfunction. Parvovirus occurs in up to 23% of renal transplant recipients with severe anemia, and 80% of infections occur within the first 3 months of transplantation. Donor transmission has been reported. Examination of bone marrow reveals typical giant proerythroblasts, and the diagnosis should be confirmed by detection of B19 virus DNA in serum by PCR assay. Some patients may have concurrent CMV disease. Treatment consists of high-dose IVIG (0.5 mg/kg per day for 5 to 10 days), reduction of immunosuppression, and, if possible, discontinuation of tacrolimus therapy for recurrent or persistent disease.

West Nile Virus

The clinical manifestation of WNV in the immunocompetent host typically consists of 3 to 6 days of malaise, anorexia, arthralgia, vomiting, nausea, rash, and lymphadenopathy. In elderly or immunocompromised individuals, more severe neurologic manifestations can occur, including encephalitis or meningitis, mental status changes, seizures, optic neuritis, muscle weakness, flaccid paralysis, and movement disorders. Symptoms that begin in the first 2 weeks after transplantation suggest transmission through the allograft, whereas symptoms that begin later suggest community acquisition. Diagnosis is confirmed by detection of WNV IgM antibody in the serum or CSF. Treatment includes reduction of immunosuppression and supportive care. IVIG anecdotally has been associated with improvement in some severely ill transplant patients. Interferon-α-2b and ribavirin have activity *in vitro* against WNV. All transplant recipients from at-risk areas should limit the risk for mosquito exposure by using insect repellents and insecticideimpregnated long-sleeved clothing while outdoors during summer months.

Human Papillomavirus

Human papillomavirus causes cutaneous and anogenital warts and is associated with cervical intraepithelial neoplasia, squamous cell carcinoma, and anogenital carcinoma.

Premalignant skin and cervical lesions are more common and progress more rapidly to cancer among organ transplant recipients. Cutaneous warts, keratotic skin lesions, and anogenital warts should be monitored and referred for early dermatologic or colorectal evaluation, biopsy, and treatment. Treatments include topical keratolytic and caustic agents, topical and oral retinoids, imiquimod, podophyllin, 5-fluorouracil, bleomycin, physical ablation, and investigational immunotherapies.

PARASITES

Toxoplasmosis

Toxoplasma gondii is a parasitic zoonosis that may cause disease in patients with deficiencies in T-cell-mediated immunity, such as renal transplant

recipients. The disease can manifest as fever, lymphadenopathy, leukopenia, encephalitis, pneumonia, endocarditis, and hepatitis. It progresses to sepsis and death if treatment is not initiated. Seronegative recipients are at risk for disease if they receive an organ from a seropositive donor. Protection against disease is obtained when using trimethoprim-sulfadoxine or dapsone as *Pneumocystis* prophylaxis. Diagnosis is made using PCR-based strategies, by demonstration of the parasite in tissue samples, or by classic radiologic findings for central nervous system disease. First-line treatment consists of pyrimethamine, folinic acid, and either sulfadiazine or clindamycin. Multiple alternative treatment regimens exist.

Selected Readings

Asberg A, Humar A, Rollaq H, et al. Oral valganciclovir is non inferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 2007;7:2106-2113.

Avery RK, Michaels M. Update on immunization in solid organ transplant recipients: what clinicians need to know. Am J Transplant 2008;8:9-14.

Fishman JA. Infections in organ-transplant recipients. N Engl J Med 2007;357:2601-2614.

Green M, Avery R, Preiksaitis J. Guidelines for the prevention and management of infectious complications of solid organ transplantation. Am J Transplant 2004;4(Suppl 10):6-165.

Hartmann A, Sagedal, S, Hjelmesaeth, J. The natural course of cytomegalovirus infection and disease in renal transplant recipients. Transplantation 2006;82:S15-

S17.

Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408-415.

Hodson EM, Jones CA, Strippoli GFM, et al. Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev 2007;CD005129.

Kang YA, Lee HW, Hwang SS, et al. Usefulness of whole-blood interferon-gamma assay and interferon-gamma enzyme-linked immunospot assay in the diagnosis of active pulmonary tuberculosis. Chest 2007;132:959-965.

Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347:2020-2029.

Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 2004;4:611-620.

Scharpe J, Evenepoel P, Maes B, et al. Influenza vaccination is efficacious and safe in renal transplant patients. Am J Transplant 2007;7:1-6.

Zar FA, Bakkangari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile-associated* diarrhea, stratified by disease severity. Clin Infect Dis 2007;45:302-307

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation*, *5th Edition*

12

Kidney Transplantation and Liver Disease

Fabrizio Fabrizi

Suphamai Bunnapradist

Paul Martin

Liver disease, most notably caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), remains a major cause of morbidity and mortality in long-term survivors of renal transplantation. Appropriate evaluation of the renal transplant candidate with chronic viral hepatitis includes assessment of viral replication, liver histology, and consideration of antiviral therapy. HCV infection is also implicated in post-transplantation graft dysfunction.

The routine assessment of the renal transplant candidate includes standard liver function tests in addition to serologies to detect HBV and HCV infection. The differential diagnosis of hepatic dysfunction in the adult renal transplant candidate includes chronic viral hepatitis as well as the full spectrum of liver diseases in patients often suffering from comorbid conditions such as diabetes and who, in addition, are typically receiving a variety of medications. Considerations include nonalcoholic fatty liver disease (NAFLD) related to diabetes mellitus and hyperlipidemia; drug hepatoxicity; passive hepatic dysfunction due to congestive heart failure; and chronic viral hepatitis. Chronic viral hepatitis, especially HCV, remains common in dialysis patients and is a major cause of morbidity and mortality in long-term survivors of renal transplantation. HCV infection is also implicated in graft dysfunction and new-onset diabetes after transplantation. Appropriate evaluation of the renal transplant candidate with chronic viral hepatitis includes assessment of viral replication and liver histology. Several innovative antiviral medications have been introduced to expand the options available to treat chronic viral hepatitis in this population.

RENAL TRANSPLANT RECIPIENTS WITH VIRAL HEPATITIS

Hepatitis B

Diagnostic Tests and Their Interpretation

Table 12.1 describes diagnostic tests for hepatitis B virus and their interpretation. Serum hepatitis B surface antigen (HBsAg) is the first detectable serum marker in acute HBV infection. After an incubation period of up to 140 days, the patient may develop symptoms such as malaise and anorexia, or become frankly icteric. By this time, other serum markers of HBV infection appear, including antibody to the hepatitis B core antigen (anti-HBc). Hepatitis B core antigen (HBcAg) is present exclusively in nuclei of infected hepatocytes, but the corresponding antibody circulates in blood. During acute HBV infection, anti-HBc antibody is predominantly immunoglobulin M (IgM). Over the subsequent 6 months, IgM levels decline, whereas IgG anti-HBc levels persist. Although anti-HBc is not a neutralizing antibody, it is the most durable marker of prior HBV infection. With successful resolution of acute HBV, protective antibody against HBsAg (anti-HBs) appears, signifying immunity against HBV. Anti-HBs antibody tends to decline and even disappear over time, leaving an "isolated" core antibody (IgG anti-HBc) as the only marker of prior HBV infection. If

HBsAg persists for more than 3 months, HBV DNA and hepatitis B e antigen (HBeAg) levels should be checked to assess level of active viral replication.

TABLE 12.1 Tests for Hepatitis B Virus

Tests		**Interpretation**
HBsAg	Hepatitis B surface antigen	HBV infection
IgM Anti-HBc	Antibody to hepatitis B core antigen	Acute or recent HBV infection
IgG Anti-HBc	Antibody to hepatitis B core antigen	Chronic or remote HBV infection

HBsAb	Antibody to hepatitis B surface antigen	Immunity to HBV (vaccine induced or a result of prior infection)
HBe	Hepatitis B e antigen	Active replication
HBV DNA	HBV viremia	Active replication

Natural History

Only about 5% of infected immunocompetent adults fail to recover from acute hepatitis B infection and develop chronic hepatitis B. In these individuals, HBsAg persists in serum, and anti-HBs fails to appear. Chronicity is more likely in individuals with impaired immune response such as uremic patients, elderly patients, and children. Symptomatic acute HBV with jaundice is more likely to lead to successful clearance of HBV infection than a subclinical acute HBV. This apparent paradox is explained by the prominent role host immunity plays in the expression of the clinical course of HBV. The immune response during icteric acute HBV infection results in more liver injury with more symptoms, but also a greater likelihood of recovery compared with symptomatically milder acute HBV. Two phases of chronic HBV infection can be distinguished. In the early months and years of chronic HBV infection, the “replicative” phase occurs, which is often accompanied by necroinflammatory changes in the liver and elevated aminotransferase levels in serum. The “replicative phase” is characterized by active viral replication: HBeAg and high titers of HBV DNA are detectable in serum. The second phase of chronic HBV infection is the “nonreplicative” phase, which is often heralded by a transient increase in aminotransferase levels. The nonreplicative phase follows HBeAg clearance. With HBeAg loss, antibodies to HBeAg appear in serum, HBV DNA levels decrease, and, generally, liver disease activity subsides both biochemically and histologically. After HBeAg clearance, infectivity is much reduced, but low levels of HBV DNA may persist for variable periods of time. Patients with persistent HBsAg positivity and normal serum aminotransferase activity were previously defined as *healthy carriers* of HBV but are now referred to as *inactive carriers*. Although these patients usually have persistently normal alanine transaminase (ALT) and aspartate transaminase (AST) levels and absent or lower serum HBV DNA (<2000 IU/mL), they still are at risk for developing progressive liver disease triggered by immunosuppression after renal transplantation. The HBV genome shows significant

heterogeneity and various mutant forms of HBV have been identified in which amino acid substitutions at crucial sites in the viral genome occur. An important subset of patients clear HBeAg and develop the corresponding anti-HBe antibody, but they continue to have active replication with strongly positive serum HBV DNA with elevated transaminases. This

HBeAg-negative form of chronic HBV is characterized clinically by a more poorly sustained response to antiviral therapy than is found in chronically infected patients who remain HBeAg positive. The HBeAg-negative form of chronic HBV, a later stage of chronic HBV infection, is becoming more prevalent as vaccination programs reduce the incidence of acute HBV infection.

HBV infection is a major cause of morbidity, with as many as 350 million people infected worldwide, resulting in an estimated 1 million deaths per year. Despite the availability of a vaccine since the early 1980s, HBV remains a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Large-scale immigration to Western Europe and North America from areas of higher prevalence of chronic HBV such as such Asia and sub-Saharan Africa has resulted in reservoirs of HBV infection in areas with large immigrant populations. Eight HBV genotypes have been identified (A to H). Specific HBV genotype may be associated with more severe liver disease; for instance, genotype C, common in Asians, confers a high risk for the development of cirrhosis and hepatocellular carcinoma. HBV genotyping is increasingly being recommended in routine clinical practice to guide management.

Prevention of HBV acquisition in dialysis centers has been an important aspect of its management in patients with chronic kidney disease (CKD). The incidence and prevalence of HBV infection in dialysis patients in developed countries has fallen since the mid-1970s as a result of strict attention to relatively simple precautions. Outbreaks of HBV infection in dialysis units are now usually a result of nonadherence to these precautions, which include serologic surveillance, isolation of HBV-infected patients, use of dedicated dialysis machines, and rigorous disinfection. HBsAg rates remain higher in patients on dialysis in less developed countries where HBV remains prevalent in the population as a whole. Despite the availability of HBV vaccination since the early 1980s, recent surveys in the United States reveal that many patients on chronic dialysis have not been vaccinated. Although response to vaccination with development of protective levels of anti-HBs is not universal in this population, at least 60% of chronic dialysis patients do respond adequately. Hepatitis B vaccine should be recommended in all candidates with no previous exposure, and anti-HBV titer should be checked to confirm immunity. Subcutaneous administration or higher or repeated doses should be considered in patients with inadequate response. Periodic antibody testing should be considered because of a higher rate of loss of anti-HBs in uremic patients.

Disease Progression After Renal Transplantation

The prevalence of HBV infection among renal transplant candidates has decreased because of less HBV infection in the dialysis population. Because of concern about post-transplantation progression of liver disease, HBV infection had been regarded as a relative contraindication to renal transplantation. HBV infection in transplant recipients may be associated with only minor elevations of aminotransferase levels despite histologic progression. Known risk factors for progression of HBV-related liver disease include alcohol use; longer duration of infection; high serum levels of HBV DNA; genotype C; coinfection with hepatitis C and D; HIV infection; and immunosuppression. Immunosuppression may increase HBV replication by various mechanisms, including diminished activity of cytotoxic T lymphocytes. In addition, the HBV genome contains a glucocorticoid-responsive element that augments HBV replication. Azathioprine and the calcineurin inhibitors may also enhance HBV replication.

The adverse effect of immunosuppressive therapy on HBV infection has been recognized in several clinical settings. Severe, even fatal, HBV reactivation is noted in patients who receive systemic chemotherapy. Reactivation of HBV

has been observed in renal transplant recipients whose prior markers of HBV infection had resolved with reappearance of HBsAg in serum despite its absence before transplantation. Liver transplantation in HBV-infected patients is associated with frequent graft reinfection followed by progressive liver disease if immunoprophylaxis is not given.

The adverse effect of HBsAg positivity on patient survival in renal transplant recipients is well established. The effect of HBsAg status on graft survival is less clear, although early reports had suggested that graft survival might be enhanced in HBV-infected recipients as a result of a diminished immune response resulting from chronic viral infection.

Role of Pretransplantation Liver Biopsy

Figure 12.1 illustrates an approach to the kidney transplant candidate with a diagnosis of HBV. Liver biopsy should be incorporated in the evaluation of renal transplant candidates with HBsAg because it is difficult, on clinical grounds alone, to estimate the severity of liver disease in CKD patients. Aminotransferase levels may be spuriously normal despite necroinflammatory changes on biopsy. Desmopressin acetate (DDAVP) should be administered by intravenous infusion at the time of biopsy to counteract uremic platelet dysfunction. A decision concerning transplant candidacy in HBsAg-positive patients should be based on both liver histology and evaluation of HBV replication by serum markers (i.e., HBeAg and HBV DNA). The absence of serum marker of replication, that is, HBV DNA or HBeAg positivity, before transplantation, however, does not preclude reactivation of HBV infection after transplantation. Patients with established cirrhosis (stage IV) on liver biopsy are at risk for frank hepatic decompensation after transplantation, and kidney transplantation alone without

simultaneous liver transplantation is contraindicated. In patients with

intact renal function, antiviral therapy with suppression of HBV replication leads to regression of even advanced fibrosis. In transplant candidates with active HBV replication, pretransplantation antiviral therapy should be initiated to prevent disease progression by suppressing HBV replication. In patients with histologically mild liver disease, renal transplantation is not contraindicated. However, even histologically mild disease can progress once immunosuppression is introduced. The advent of effective oral antiviral therapy can prevent post-transplantation progression of HBV. If the initial liver biopsy shows extensive fibrosis and there is active HBV replication, repeat liver biopsy should be considered after a year or more of antiviral therapy to determine whether regression of liver fibrosis has occurred. All patients with HBV should be placed on antiviral therapy after transplantation to avoid reactivation of HBV replication and progression of liver disease.

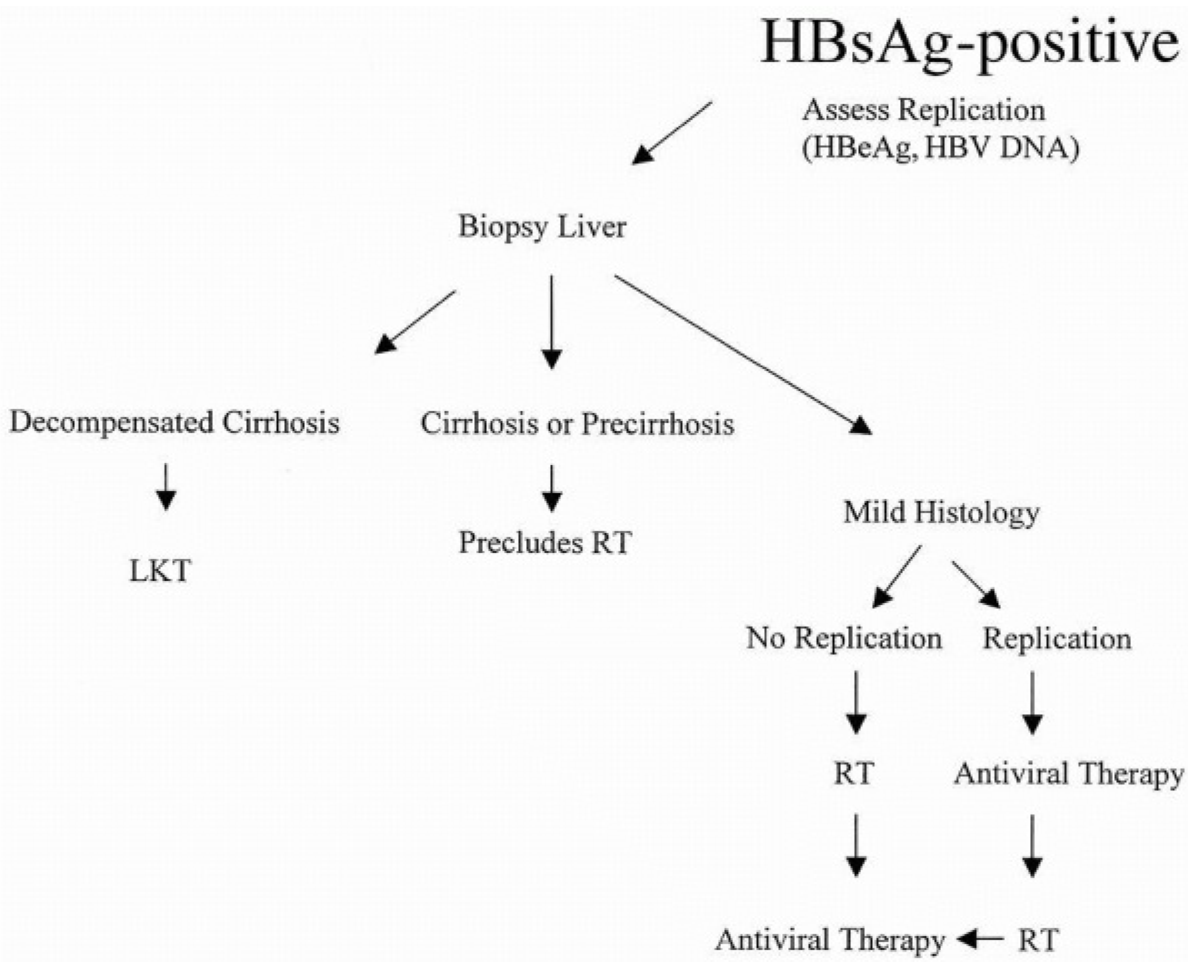


FIGURE 12.1 Approach to the workup of the kidney transplant candidate with viral hepatitis B. HBV, hepatitis B virus; LKT, combined liver and kidney transplant; RT, renal transplant.

Advances in Antiviral Therapy

The options for antiviral therapy have expanded with several licensed oral agents in addition to interferon (IFN). Although IFN and pegIFN are efficacious in the treatment of chronic HBV, their use is contraindicated in renal transplant recipients because the immunomodulatory actions of IFN may lead to the precipitation of severe and often irreversible graft dysfunction.

The introduction of lamivudine was a major advance in the management of post-transplantation HBV-related liver disease. Lamivudine is a nucleoside analogue that suppresses HBV replication by interfering with the reverse transcriptase activity of HBV, causing termination of the proviral DNA chain. Lamivudine suppresses HBV replication and improves aminotransferase levels in renal transplant recipients. Lamivudine is well tolerated, is administered orally, and has no adverse immunomodulatory activity. Because lamivudine is metabolized by the kidney, the dose should be reduced in patients with impaired renal function. The standard dose is 100 mg once daily, which is reduced to 50 mg daily for a creatinine clearance of 30 to 49 mL per minute. Prolonged use of lamivudine is associated with the development of drug resistance, as a consequence of the induction and selection of HBV mutants at the YMDD motif of DNA polymerase, which may cause clinical worsening of liver disease. Because of the high rate of antiviral resistance, lamivudine has been superseded as a first-line agent for treatment of HBV. Newer choices include entecavir, which shares cross-resistance with lamivudine, and tenofovir, which does not. Dose reductions may be necessary if renal insufficiency is present.

Hepatitis C

Interpretation of Diagnostic Tests

Table 12.2 describes diagnostic tests for HCV and their interpretation. Serologic testing is the initial mode for diagnosis of HCV infection. Third-generation enzyme-linked immunoabsorbent assays (ELISAs) have been introduced and have further enhanced specificity and sensitivity of serologic testing, including in patients with end-stage renal disease (ESRD). The gold standard for the diagnosis of HCV remains the detection of HCV viremia (HCV RNA) in serum by reverse-transcriptase polymerase chain reaction (PCR). This assay has effectively replaced the recombinant immunoblot assay. More recently, transcriptionmediated amplification (TMA), another highly sensitive techniques to detect HCV RNA have been introduced. Because of the occurrence of HCV viremia in a small minority of patients with CKD who are negative by serologic testing, a PCR or TMA test should be performed if there is unexplained transaminitis or if a clinical concern about HCV infection remains despite negative serologic tests.

TABLE 12.2 Tests for Hepatitis C Virus

Tests	Uses	Comments
Anti-HCV ELISA 3.0	Initial diagnosis	Excellent sensitivity
HCV PCR qualitative TMA	Confirmation of HCV infection	Helpful in dialysis of seronegative patients
HCV PCR quantitative	Assessment of viral load	Less sensitive than qualitative tests; more reproducible than qualitative tests; useful for monitoring response to IFN
HCV genotyping	Treatment decision	Role in predicting reSponsiveness to IFN

ELISA, enzyme-linked immunosorbent assay; IFN, interferon; PCR, polymerase chain reaction.

Natural History

Chronic HCV infection remains prevalent in the hemodialysis population despite elimination of HCV from the blood supply, reflecting, in part, nosocomial spread in hemodialysis units. HCV infection and its potential complications are a frequent cause of concern in potential renal transplant recipients.

Because the natural history of HCV extends over decades rather than years, adverse

consequences of chronic HCV infection in patients followed for a short period of time may not be apparent. CKD patients have higher morbidity and mortality rates than do the general population because of their comorbidities such as diabetes and systemic hypertension. As a result, the long-term consequences of HCV infection have been difficult to assess in this population. Evaluation of HCV infection in renal transplant candidates is further complicated by the observation that aminotransferase levels in the dialysis population are usually lower than the nonuremic population. Dialysis patients who are HCV viremic have aminotransferase levels greater than those who are not HCV viremic, although typically, the values are still within the normal range.

Six major HCV genotypes have been described; they differ little in clinical expression but vary in their responsiveness to IFN therapy. Response rates among patients with genotype 1 are much lower than in patients with HCV genotypes 2 and 3.

Disease Progression After Renal Transplantation

The frequency of HCV infection among renal transplant recipients is influenced by various factors, including prior blood transfusion, history of previous transplantation, type and duration of pretransplantation renal replacement therapy, and geographic origin of the recipient. Most anti-HCV-seropositive renal transplant recipients have persistent HCV viremia. HCV RNA titers may increase markedly as a result of post-transplantation immunosuppression. Post-transplantation HCV-related liver disease is often progressive in renal transplant recipients. Factors implicated in more rapid progression of HCV include alcohol abuse and HBV coinfection. Liver disease was more aggressive in recipients who acquired HCV at the time of transplantation before screening for HCV was available because they developed an acute hepatitis at a time of maximum immunosuppression. It is unclear whether choice of initial calcineurin inhibitor affects the progression Although cyclosporine at high concentrations has an inhibitory effect on HCV replication, the benefit of

---

cyclosporine over tacrolimus in the clinical setting remains to be confirmed. Azathioprine and antilymphocyte agents to treat rejection have been implicated in more severe liver disease in HCV-infected recipients. Administration of high-dose steroids and antilymphocyte antibodies should be avoided and only used after a critical evaluation of potential risk and benefit, especially the risk for accelerating the course of liver disease.

Detailed studies with adequate follow-up have documented an adverse effect of HCV infection on patient survival after kidney transplantation alone and after combined kidney-pancreas transplantation. However, the outcome of HCV-infected hemodialysis patients is worse than for matched patients who undergo transplantation. Recipients of a first deceased donor transplant have an initially greater perioperative risk for death than those who remain on dialysis therapy but a subsequent long-term benefit. Glomerulonephritis and mixed cryoglobulinemia have also been described after

transplantation and can lead to graft loss.

HCV infection is associated with an increased risk for new-onset diabetes after transplantation (NODAT) a risk factor for recipient death and graft loss. In HCV-positive renal transplant recipients, an overall incidence of NODAT of close to 40% has been described. The incidence is even higher if tacrolimus is used for immunosuppression and if other risk factors are present (see Chapter 10). HCV-positive transplant candidates should be warned of this increased risk.

Role of Pretransplantation Liver Biopsy

Figure 12.2 illustrates an approach to the evaluation of renal transplant candidates with HCV. Liver biopsy is essential in the evaluation of liver disease in renal transplant candidates because reliance on clinical and biochemical findings may underestimate its severity. Pretransplantation liver biopsy provides useful prognostic information. Patients with minimal to mild chronic hepatitis (stages I and II) can proceed safely to transplantation. Pretransplantation treatment of hepatitis C should be considered with the potential benefits of aborting progression of liver disease and protecting the graft against HCV-related glomerulonephritis. Patients with cirrhosis on biopsy should not be offered isolated renal transplantation because of the risk for post-transplantation hepatocellular failure. However, if there is a sustained virologic response to antiviral therapy, and if repeat liver biopsy shows regression of fibrosis, transplant candidacy can be reconsidered. For cirrhotic patients, combined liver-kidney transplantation is a consideration if they subsequently develop hepatocellular failure (see "Kidney and Liver Transplantation"). For patients whose histology precludes renal transplantation yet whose hepatic function is too well compensated to require liver transplantation, it may be safer to remain on dialysis. In the event that decompensated cirrhosis develops, combined orthotopic liver-kidney transplantation may be indicated (Table 12.3).

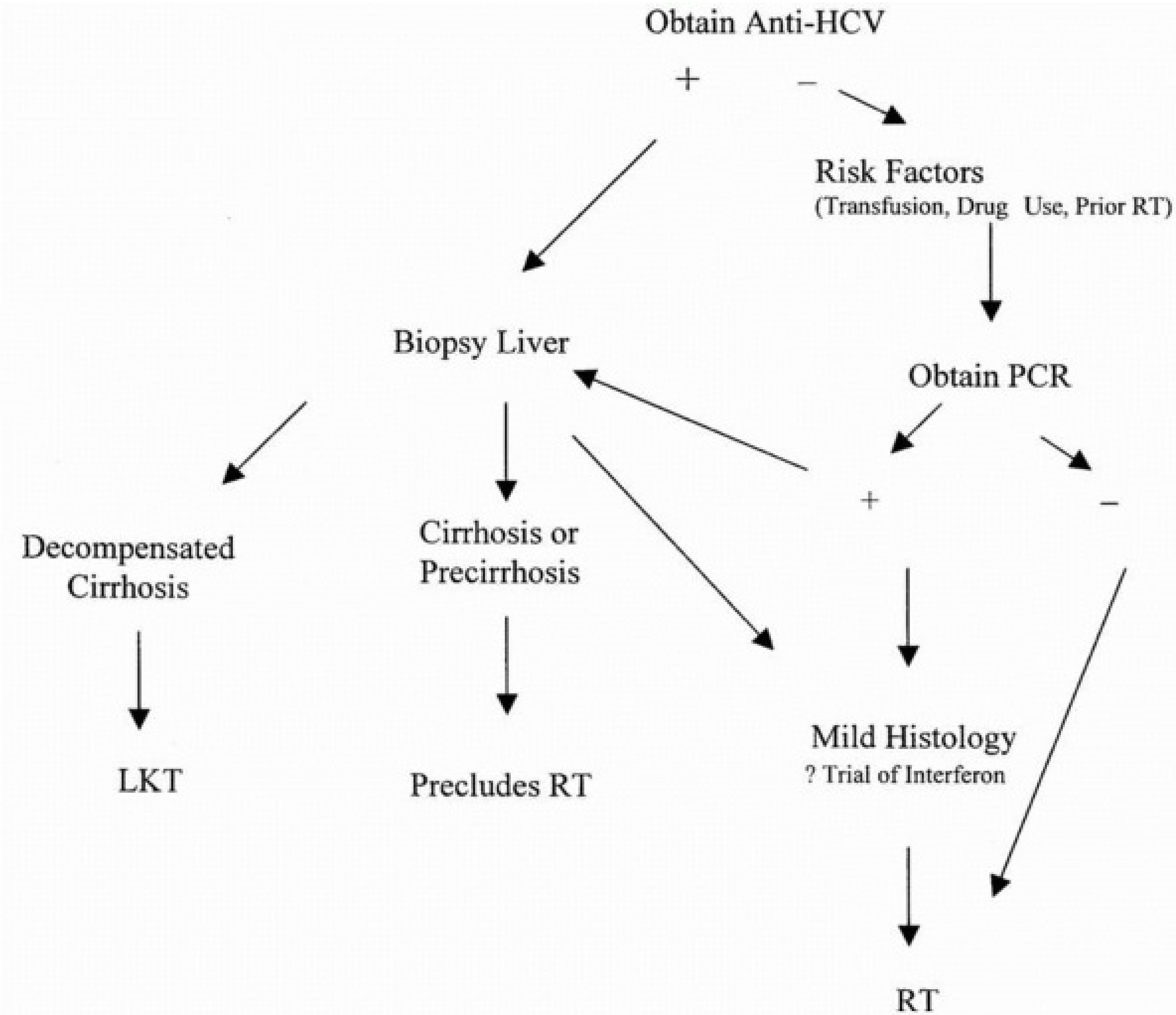


FIGURE 12.2 Approach to the workup of the kidney transplant candidate with viral hepatitis C. HCV, hepatitis C virus; LKT, combined liver and kidney transplant; RT, renal transplant.

TABLE 12.3 Indications for Combined Kidney and Liver Transplantation

Orthotopic liver transplant (OLT) candidate with severe irreversible renal dysfunction caused by:

1. Polycystic kidneys with massive hepatomegaly

2. Primary oxalosis

3. Prolonged pre-OLT dialysis dependence

4. Glomerulonephritis (especially as a consequence of IgA, HBV, and HCV)

5. Repeat OLT with calcineurin inhibitor toxicity

6. Diabetic nephropathy

Status of Antiviral Therapy

The main goal of treatment is to induce sustained virologic response (SVR) and reverse fibrosis. Many factors influence response to treatment, including the degree of inflammation, levels of AST and ALT, and most importantly, specific HCV genotype. The major concern limiting the post-transplantation use of IFN is the risk, noted earlier, of precipitating graft loss. However, successful pretransplantation antiviral therapy for HCV has been followed by a durable absence after transplantation of HCV RNA viremia. To enhance the likelihood of a sustained virologic response, IFN needs to be administered in combination with ribavirin. However, ribavirin needs to be used very cautiously if at all in patients with renal insufficiency because it causes hemolytic anemia, and its metabolites are not cleared by dialysis. Antiviral therapy in this population should only be undertaken by physicians skilled in the management of HCV.

OTHER CAUSES OF LIVER DISEASE IN RENAL TRANSPLANT RECIPIENTS

Viral infections, such as herpes simplex virus (HSV) and cytomegalovirus (CMV), and drug hepatotoxicity should be considered in the differential diagnosis of post-transplantation hepatic dysfunction. Patients with elevated levels of serum aminotransferases or γ-glutamyl transpeptidase should be questioned about ingestion of alcohol and hepatotoxic drugs. Specific inquiry should be made about use of herbal and health food store products. Serum aminotransferase and γ-glutamyl transpeptidase levels should be rechecked after the patient has abstained from potential toxic

substances. A low-grade, transient

elevation of serum aminotransferases is commonly seen in patients receiving calcineurin inhibitors. If these elevations persist or are more marked, a thorough workup, including liver biopsy, is indicated.

In the 1970s and 1980s, hemosiderosis was common in patients with ESRD. The widespread use of erythropoietin and the lowered requirement for blood transfusion have made hepatic iron overload less common in both dialysis patients and transplant recipients. Quantitative iron determined on liver biopsy and genetic testing for hemochromatosis may be necessary to confidently distinguish primary hemochromatosis from secondary ion overload.

Another form of liver disease receiving increased attention is nonalcoholic fatty liver disease. Important predisposing factors for this condition include obesity, hyperlipidemia, and diabetes mellitus. Diagnosis is by liver biopsy, and management involves correcting the precipitating factors.

An important consideration in a transplant recipient with unexplained hepatic dysfunction is viral hepatitis acquired from the donor graft. This should be excluded by appropriate serologic workup. Intermittent hepatic dysfunction may result from biliary colic, and pain might not be prominent in older patients. Ultrasound is the initial investigation.

THE KIDNEY DONOR WITH POSITIVE HEPATITIS SEROLOGIES

Effects on Recipient

Donor HBsAg positivity precludes kidney donation. The use of organs from HBsAg-negative, anti-HBc antibody-positive deceased donors has the potential to transmit HBV infection because of amplification of minute quantities of residual HBV DNA by immunosuppression. The rate of transmission is significantly higher in hepatic recipients than in other solid organ recipients. In contrast, use of a renal graft from an IgG anti-HBc antibody-positive donor is associated with a very low risk for infection transmission, and these kidneys can be safely considered for donation, especially for recipients who have been successfully immunized with HBV vaccine. If an anti-HBc (“core”)-positive organ is used in an HBV-naive recipient, considerations include use of long-term oral antiviral prophylaxis. If the potential donor is IgM anti-HBc positive, recent acute HBV is likely even in the absence of HBsAg, and there is a greater risk for HBV transmission; thus, the graft should be declined.

Transmission of HCV by renal transplantation has been unequivocally demonstrated with occasionally severe acute, even fatal, hepatitis. There are wide variations in the rate of transmission of HCV from anti-HCV-positive donors, which may be a result of several factors, including donor HCV viral load and the technique used for preservation

of donor grafts. The rate of transmission of HCV from HCV-infected donors appears to be much higher if flush preservation instead of pulsatile perfusion is used. The role of genotyping of donor and recipient are less well established.

Transplantation of kidneys from anti-HCV-positive donors into anti-HCV-positive recipients is safe in the short term. However, among anti-HCV-positive recipients, those who received anti-HCV-positive kidneys may have a somewhat worse survival rate than did recipients of anti-HCV-negative kidneys. HCV infection is more common in deceased donors than in the general population. For an HCV-positive transplant candidate, the waiting time for a kidney may be greatly foreshortened by the acceptance of a kidney from a HCV-positive donor. Because survival following renal transplantation is enhanced compared with survival on chronic dialysis, it may be more advantageous for an HCV-positive transplant candidate to accept an HCV-positive graft after a short wait than to accept an HCV-negative kidney after a protracted wait. The benefits and risks of accepting an HCV-positive graft must be carefully discussed with HCV-positive transplant candidates.

KIDNEY AND LIVER TRANSPLANTATION

Combined Liver and Kidney Transplantation

About 20% of patients undergoing orthotopic liver transplantation (OLT) have clinically significant preoperative renal insufficiency, and about 2% of patients undergo a combined liver-kidney transplant (LKT). Most patients with pre-OLT renal dysfunction do not require concomitant kidney transplantation because their renal dysfunction is potentially reversible. A diagnosis of the hepatorenal syndrome or acute tubular necrosis is not an indication for LKT, although patients with pre-OLT dialysis dependence for more than several weeks may develop irreversible parenchymal changes that might limit their capacity for recovery. Table 12.3 lists the common indications for LKT. Graft and patient survival rates are lower in patients requiring LKT than in patients receiving a kidney transplant alone, primarily because of the high mortality rate during the first 3 post-transplantation months as a consequence of increased surgical risk and other comorbid conditions. However, if survival data are censored for patients who died during the first 3 months, long-term graft and patient survival rates of LKT and kidney transplant alone are similar. The kidney transplantation adds little to the morbidity of the concomitant OLT.

Liver transplantation appears to provide a form of immunologic protection to concomitantly transplanted organs. This allograft-enhancing effect of the liver on other transplanted organs from the same donor can be demonstrated even for patients with a positive pretransplantation crossmatch. Several immunologic mechanisms for this phenomenon have been proposed, including the development of anti-idiotypic antibodies to major histocompatibility complex (MHC) class I and class II antibodies, the

absorption of lymphocytotoxic antibodies onto reticuloendothelial cells of the liver allograft, and a soluble MHC class I molecule, which is principally made in the liver, that may inhibit cytotoxic T-lymphocyte activity. Another important mechanism may be the development of hematopoietic chimerism occurring after liver transplantation, resulting in tolerance.

There are practical implications to the protective effect of the concomitant liver transplantation. It is not necessary to routinely crossmatch unsensitized patients before LKT. If the crossmatch is positive in a sensitized patient, the LKT may not necessarily be contraindicated, and some programs progress with transplantation with addition of a perioperative infusion of intravenous immune globulin (see Chapter 5). The aggressiveness of immunosuppression after liver transplantation alone is generally less than that after other organ transplantations, and fear of recurrent disease is greater than the fear of rejection. The immunosuppressive protocol after LKT is generally less intense than that after kidney transplantation alone. Calcineurin inhibitor dosage and blood levels are kept lower, and antibody-depleting agents are avoided for fear of an increased risk for infection and recurrence of hepatitis. The incidence of acute rejection after LKT is low.

Allocation of Liver Transplants

Kidney transplant allocation has long been based on waiting time and human leukocyte antigen matching (see Chapter 4), but not on disease severity or patient prognosis. Liver transplants are allocated based on disease severity. The Model of End-Stage Liver Disease (MELD) score is a formula that gives points to objective laboratory parameters (serum bilirubin, international normalized

---

ratio, serum creatinine) that have been shown to predict survival. The higher the MELD score, the greater the chances of liver allocation. The inclusion of the creatinine in the MELD score means that liver transplant candidates with pretransplantation renal impairment are more likely to be allocated a liver. For LKT recipients, it is the MELD score that determines allocation and not the kidney allocation algorithm. Thus, paradoxically, candidates for a double-transplant LKT are likely to wait much less time for their kidney than candidates “only” waiting for a kidney.

Kidney After Liver Transplantation

Chronic renal failure develops in close to 20% of OLT recipients at 5-year follow-up and is associated with an increased risk for death after transplantation. The etiology of renal failure is typically multifactorial and includes preexisting renal disease, perioperative renal damage, calcineurin inhibitor therapy, nephrotoxic effects of other drugs, hypertension, HCV with associated glomerulonephritis, and diabetes mellitus. Renal transplantation may be a consideration in otherwise robust OLT recipients who develop ESRD.

Selected Readings

Bahirwani R, Campbell MS, Siropaides T, et al. Transplantation: impact of pretransplant renal insufficiency. Liver Transplant 2008;14:665-671.

Dube GK, Cohen DJ. Simultaneous liver and kidney transplantation. Curr Opin Nephrol Hypertens 2007;16:547-553.

Eason JD, Gonwa TA, Davis CL, et al. Proceedings of Consensus Conference on Simultaneous Liver Kidney Transplantation (SLK). Am J Transplant 2008;8:2243-2251.

Gonwa TA, McBride MA, Anderson K. et al. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLTX) in the US: where will MELD lead us? Am J Transplant 2006;6:2651-2659.

KDIGO Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in Chronic Kidney Disease: Management of HCV-infected patients before and after. Kidney Int 2008;73:S53-S68.

Mahmoud IM, Elhabashi AF, Elsawy E, et al. The impact of hepatitis C virus viremia on renal graft and patient survival: a 9-year prospective study. Am J Kidney Dis 2004;43:131-139.

Martin P, Fabrizi F. Hepatitis C virus and kidney disease. J Hepatol 2008;49:613-624.

Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931-940.

Ruiz R, Kunitake H, Wilkinson AH, et al. Long-term analysis of combined liver and kidney transplantation at a single center. Arch Surg 2006;141:735-741; discussion, 741-742.

Simpson N, Cho YW, Cicciarelli JC, et al. Comparison of renal allograft outcomes in combined liver-kidney transplantation versus subsequent kidney transplantation in liver transplant recipients: analysis of UNOS Database. Transplantation 2006;82:1298-1303.

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

13

Diagnostic Imaging in Kidney Transplantation

Allison L. Pearl

Nagesh Ragavendra

Christiaan Schiepers

The clinician evaluating a patient with renal transplant dysfunction has the choice of a variety of imaging procedures, including ultrasound (US), nuclear medicine (NM), computed tomography (CT), magnetic resonance imaging (MRI), and less commonly used today, excretory urography. Imaging evaluation is usually initiated either with duplex US, which provides anatomic imaging and some physiologic information quickly, noninvasively, and portably, or with NM studies, which provide physiologic information and less morphologic information. CT provides superb cross-sectional information but involves ionizing radiation and the use of iodinated contrast medium and lacks portability. MRI provides superb anatomic information, can noninvasively image large vessels, and can evaluate function without risk for acute renal failure. MRI, however, is not portable, is expensive, and requires special equipment for guided interventions. In addition, there is an association between MRI contrast agent use (gadolinium) and the development of nephrogenic systemic fibrosis (NSF). In this chapter, we discuss the use of each of these imaging techniques in clinical renal transplantation.

RADIOLOGIC EVALUATION OF THE LIVING DONOR

The process of evaluating a potential living donor is discussed in Chapter 7. The radiologic studies used to screen potential living donors are performed to ensure that after nephrectomy, the donor is left with an anatomically and functionally normal kidney. The number and branching pattern of the renal arteries and veins are identified. This information permits the surgeon to decide which kidney is to be removed and to determine the suitability for laparoscopic compared with open nephrectomy (see Chapter 6). The traditional donor radiologic workup typically consisted of an intravenous urogram followed by angiography. With current technologic advances in CT and MRI scanning, angiographic-type images of the kidney vasculature can be obtained without the need for catheter angiography.

Computed Tomographic Angiography, and Urography

The helical CT scan followed in the same session by a postcontrast radiograph produces a modified intravenous urogram, usually called a *computed tomographic urogram* (CTU). Helical CT allows very rapid acquisition of a volume of data, and the advent of multidetector helical CT has further improved this technique. *Computed tomographic angiography* (CTA) differs from CTU in that intravenous contrast is injected rapidly (4 to 5 mL per second), imaging sequence begins at peak contrast concentration in the aorta (20 seconds after injection). The use of very thin beam collimation (0.5 to 3 mm) yields highresolution images of vessels. The resulting volume of data can be computer rendered and displayed in a variety of ways, and made to look like a projectional radiographic angiogram. This technique can reliably delineate relevant vascular anatomy for surgical planning (Plate 13.1). This method has essentially replaced catheter angiography in most centers.

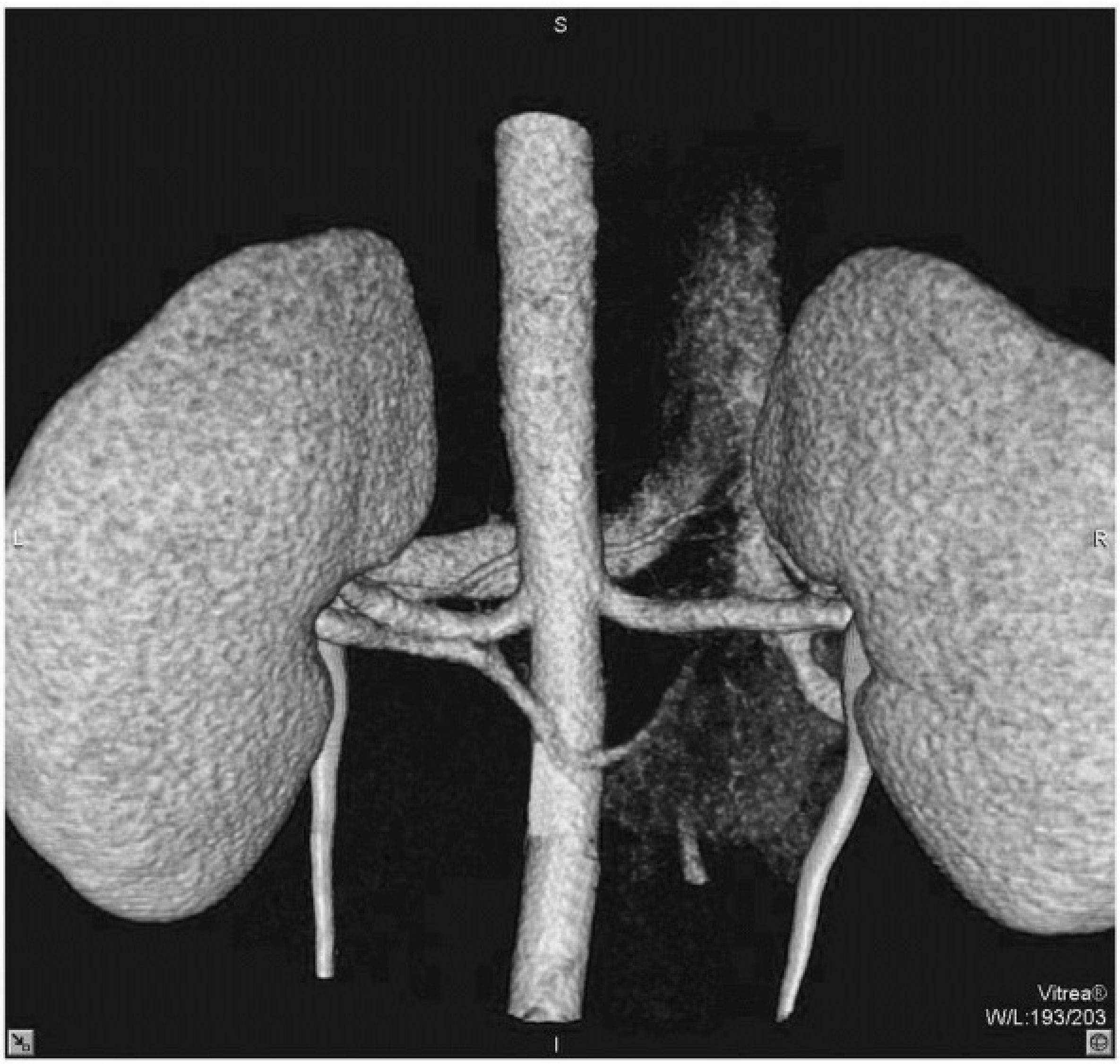


PLATE 13.1 Computed tomographic angiogram of renal arteries with volume-rendered reformation. Posterior vantage with aorta on *left*, demonstrating two left

renal arteries. see color image

The urographic images of the CTU permit an evaluation of the intrarenal collecting system, ureters, and bladder. This allows detection of anatomic variants and pathology, such as supernumerary ureters, ureteropelvic junction obstruction, papillary necrosis, calyceal diverticula, extrarenal pelves, ureteroceles, and urolithiasis.

Magnetic Resonance Angiography and Urography

MRI and MR angiography and venography can provide similar information to CT and CTA. Drawbacks include less optimal evaluation of collecting systems and insensitivity for stone detection.

RADIOLOGIC TECHNIQUES IN THE EARLY POST-TRANSPLANTATION PERIOD

The indications for radiologic investigations in the early post-transplantation period are discussed in Chapter 9.

Allograft Size

Renal transplant size increases in most acute processes and is thus a nonspecific indicator of renal dysfunction. Some studies show that an increase in graft cross-sectional area of more than 10% (measured by US) is suggestive of acute rejection, but the finding is too nonspecific to be clinically reliable. Practical use of allograft size is also limited by the fact that a normally functioning graft may be increased in size by up to 30% 2 months after transplantation. The volume of a normal renal transplant usually stabilizes by 6 months.

Collecting System Dilation

Collecting system dilation may be obstructive or nonobstructive. The degree of dilation is often expressed using a grading system (grades I to IV) for US or excretory urography, or as mild, moderate, or severe; however, both of these systems are subjective. Obstruction of the transplant collecting system may occur secondary to extrinsic processes (e.g., peritransplantation fluid collection), ureteral stricture (as a consequence of vascular insufficiency or rejection), or intraluminal lesions, such as kidney stone, blood clot, or sloughed papilla (Fig. 13.1). A mild, self-limited obstruction may result from early postoperative edema at the ureteroneocystostomy site, and minimal dilation may persist despite resolution of obstruction. Other causes of nonobstructive collecting system dilation include a full bladder, rejection, infection, and resolved, prior obstruction. This latter cause of nonobstructive dilation is particularly relevant in the transplanted kidney because the collecting system is

denervated and has no tone.

The absence of collecting system dilation does not entirely exclude the possibility of obstruction. The most reliable noninvasive method to diagnose obstruction is progressive collecting system dilation on serial sonograms. Antegrade pyelography, a mini-nephrostomy, or a Whitaker pressure-flow study may be necessary to determine whether collecting system dilation has an obstructive or nonobstructive cause.

NM imaging of ureteral obstruction typically shows normal perfusion and parenchymal uptake of tracer by the transplant, but pooling of tracer in the renal pelvis and prolonged pelvic retention. An obstructed system does not respond to the administration of diuretics such as intravenous furosemide. A system with an emptying half-time of more than 20 minutes is considered obstructed (normal emptying half-time is less than 15 minutes). Table 13.1 gives an overview of radiopharmaceuticals currently in use. The use of the resistive index (RI; see “Acute Rejection,” below) to distinguish obstructive from nonobstructive pyelocaliectasis has been proposed, but data regarding its clinical utility are inconclusive.

FIGURE 13.1 Sonogram demonstrating hydronephrosis secondary to peritransplantation fluid collection.

TABLE 13.1 Radiopharmaceuticals for Use in the Quantification and Ev Morphology

Radionuclide		Biologic Compound	Percentage	Physiologic or Biochemical Mechanism
^{99m}Tc	DTPA	Diethylenetriamine pentaacetic acid	>90	Glomerular filtration, no resorption
^{99m}Tc	MAG3	Mercaptoacetyltriglycine	>95	Tubular secretion
^{99m}Tc	DMSA	Dimercaptosuccinic acid	7-14	Excreted into urine, binds to SH groups in cortical tubule cells
^{67}Ga	Ga	Gallium citrate		Localizes in sites of inflammation and certain neoplasms
^{111}In or				Localizes in

^{99m}Tc	WBC	White blood cells		inflammatory tissue
^{111}In		Lymphocytes		Localizes in inflammatory tissue

ERPF, effective renal plasma flow; Ga, gallium; GFR, glomerular filtration rate; I, ic
blood cell count.

Peritransplantation Fluid Collections

Peritransplantation fluid collections may be produced by lymphoceles, urinomas, hematomas, and abscesses; all of these may compress the ureter and iliac veins, resulting in hydronephrosis and lower extremity edema. They all manifest as fluid collections on cross-sectional imaging studies (US, MRI, CT) or as photopenic regions on NM scans or scintigrams. Although there are imaging features suggestive of the nature of the fluid collection, their appearance is usually not sufficiently specific; imaging-guided aspiration is often necessary.

Hematomas

Hematomas are common in the immediate postoperative period; they may be extrarenal or subcapsular in location and usually resolve spontaneously. They may also occur after a biopsy or result from rupture of a graft pseudoaneurysm. On occasion, the hematoma may be large enough to obstruct the ureter. The US appearance of a hematoma varies with time, being echogenic in the acute phase and decreasing in echogenicity as clot lysis occurs. An acute hematoma is of high attenuation on CT and also decreases with time. The signal intensity of a hematoma on MRI is variable.

Urinomas

Urinomas resulting from extravasation of urine from the renal pelvis, ureter, or ureteroneocystostomy usually occur in the first 1 to 3 weeks after transplantation and may be caused by disruption of the ureterovesical anastomosis, incomplete bladder closure, ischemia of the collecting system, postbiopsy injury, or severe obstruction.

US reveals a nonspecific, usually nonseptated, fluid collection, often adjacent to the

lower pole of the transplant. The CT appearance of a urinoma is a peritransplantation fluid collection that may contain contrast-opacified fluid that is isodense to collecting system fluid if the leak is active at the time of the scan. MRI reveals a fluid collection that has identical signal characteristics to urine in the bladder. The leak may be extraperitoneal, intraperitoneal, or both, and in the latter circumstances, ascites may also be present. Characterization of the fluid can be achieved by obtaining a sample using US-guided aspiration and then determining the creatinine concentration (see Chapter 9).

Cystography is the examination of choice to confirm or exclude the bladder as the source of leak. If the bladder is not the source, the extravasation must be from above the ureterovesical anastomosis. If kidney function is adequate, a nuclear medicine study or a urogram may visualize the urinoma, although the precise location of the leak may be difficult to identify. NM imaging typically shows abnormal accumulations of activity outside the collection system (Fig. 13.2). Occasionally, this finding may be confused with ureteral stasis, in which case the abnormal accumulation will resolve when the patient voids or is given intravenous furosemide.

Lymphoceles

Lymphoceles are the most common type of peritransplantation fluid collection and are the product of extraperitoneal or renal lymphatic disruption at surgery or during graft harvesting (see Chapter 8). They usually occur several weeks to months after surgery. The incidence of lymphoceles has been reported to be higher when rapamycin is used for early post-transplantation immunosuppression. Small lymphoceles are common and are usually asymptomatic, but larger ones can cause obstruction.

The typical US appearance of a lymphocele is a fluid collection inferior and medial to the transplant that often contains septations and low-level echoes (Fig. 13.3). The MRI signal characteristics of a lymphocele tend to be of low signal intensity on T1-weighted images and of high signal intensity on T2-weighted images.

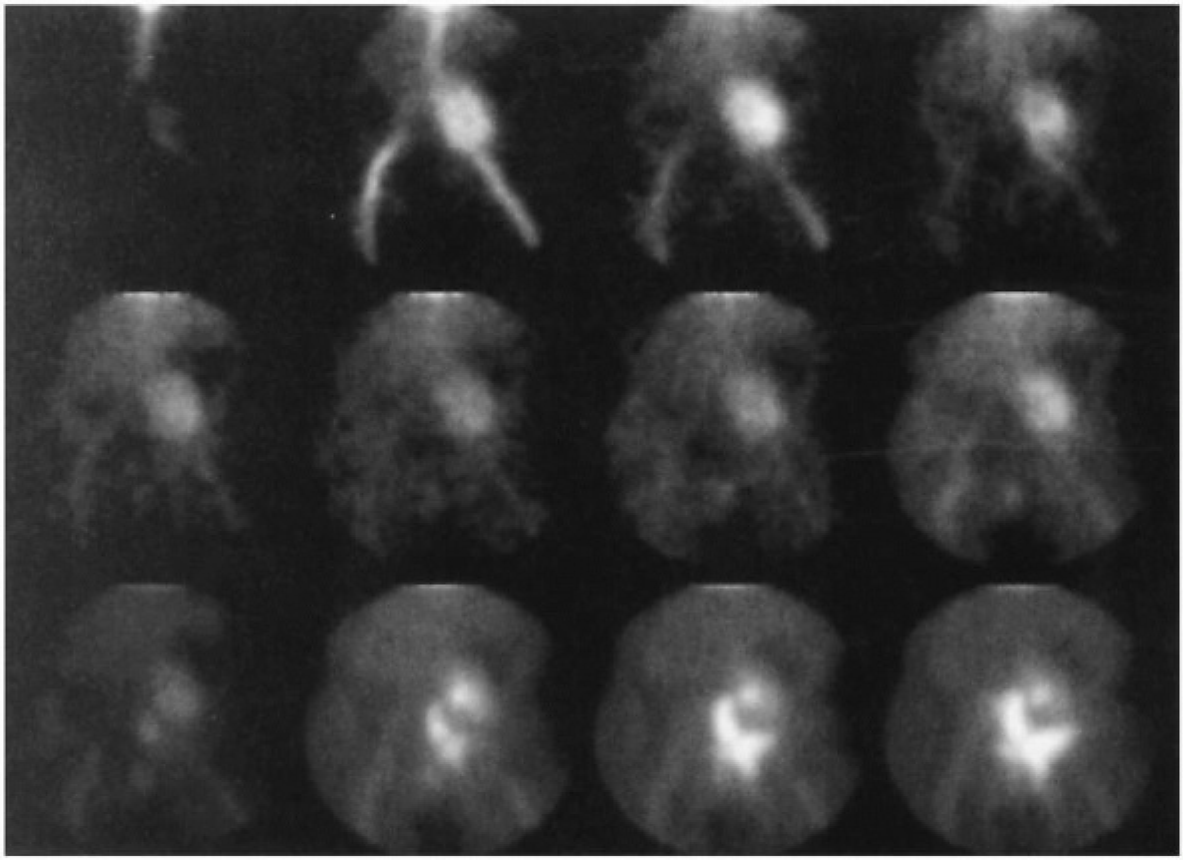


FIGURE 13.2 Nuclear medicine images of a left iliac transplant kidney (radiopharmaceutical:^{99m}Tc diethylenetriamine pentaacetic acid [DTPA]). The *top left* image shows activity in the abdominal aorta and the beginning of the transplant. The next two images show prompt visualization of the kidney, reflecting normal tracer concentration. In the *bottom row,* enlarging irregular activity is seen between the kidney and urinary bladder, indicative of urinary extravasation.

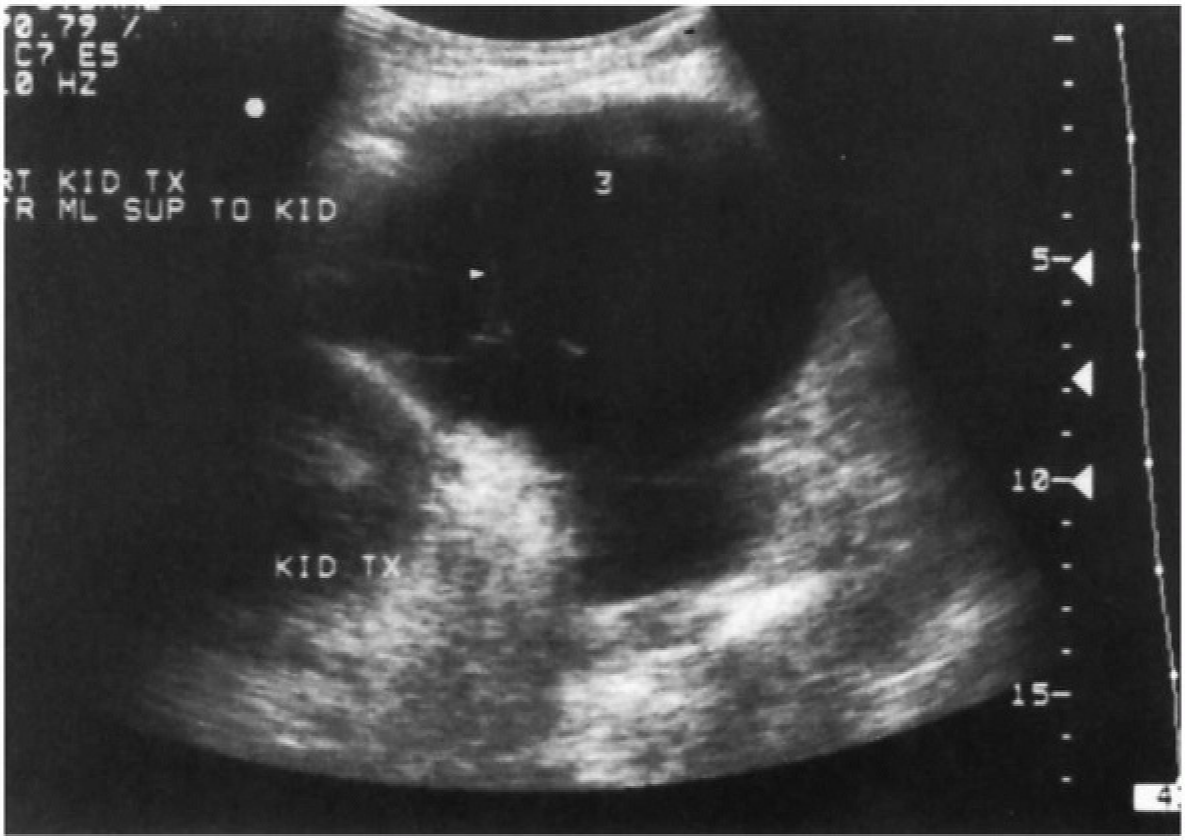


FIGURE 13.3 Sonogram demonstrating lymphocele *(3)* with septations *(arrowhead)*.

Abscesses

A peritransplantation abscess is usually secondary to infection of a preexisting fluid collection and generally occurs 4 to 5 weeks after transplantation. The US appearance is a fluid collection that contains debris, low-level echoes, and occasionally gas; the latter manifests as mobile, nondependent, echogenic foci with "dirty" shadowing or ring-down artifact.

The CT appearance is a heterogeneous fluid attenuation lesion (Fig. 13.4) that may contain gas. In the acute setting, cross-sectional imaging techniques (US, CT) enable rapid diagnosis and potential treatment of a suspected abscess by providing guidance for aspiration and drainage. The absence of any imaging features suggestive of an abscess does not exclude the presence of infection.

NM imaging employs different radiopharmaceutical agents for infection surveys. Labeled white blood cells (WBCs), lymphocytes, antileukocyte antibodies, and gallium are available for this purpose. These tracers localize in inflammatory tissue and may be helpful in detecting a renal or perirenal abscess. A rejecting transplant, however, may also "light up," and interpretation of the results needs to be approached cautiously. NM techniques are based on injection of the labeled

compound, which travels through the body and accumulates at the site of infection or inflammation. The dose administered and half-life of the attached radionuclide determine the time of imaging after injection, from 2 to 24 hours for ^{99m}Tc, 1 to 2 days for 111In, and 1 to 3 days for ^{67}Ga.

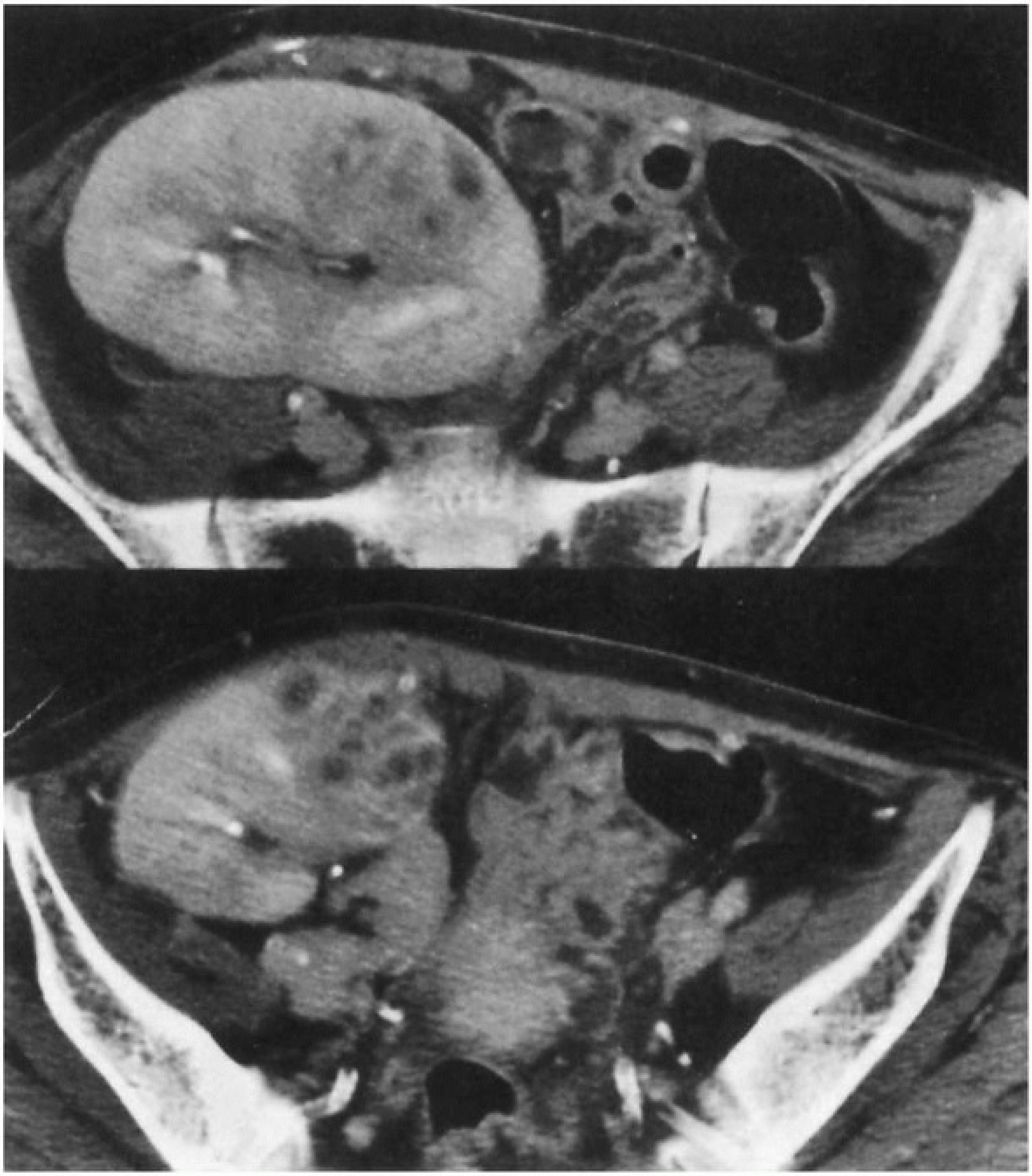


FIGURE 13.4 Abscess in a renal allograft. There is a heterogeneous mass on contrast-enhanced computed tomography. Many small compartments preclude percutaneous drainage. Renal function was surprisingly well preserved. Abscess resolved after intensive antibiotic therapy.

Acute Rejection

A variety of morphologic alterations may occur with acute rejection. All these abnormalities may be seen with other medical complications of transplantation. Because many are subjective, these findings are insufficiently sensitive or specific to diagnose rejection definitively and do not obviate the need for biopsy. The US abnormalities include graft enlargement, obscured corticomedullary definition, decreased echogenicity of the renal sinus, thickened urothelium, prominent hypoechoic medullary pyramids, increased or decreased cortical echogenicity, and scattered heterogeneous areas of increased echogenicity, the latter probably representing foci of hemorrhage (Fig. 13.5).

Resistive Index

With the advent of duplex US (combining grayscale imaging with Doppler capability), it was hoped that the physiologic parameters that could be measured with this technique would be diagnostic of rejection. The major parameter studied was vascular resistance (impedance), which is measured as the percentage reduction of the end-diastolic flow compared with the systolic flow. The resistive index (RI = peak systolic velocity [PSV] minus end-diastolic velocity divided by PSV) or the pulsatility index (PI = PSV minus end-diastolic velocity divided by the mean velocity) are often elevated in rejection (Fig. 13.6), but because any cause of renal dysfunction may increase vascular resistance in the kidney, the finding of an elevated RI itself is nonspecific. Elevation of the RI (>0.9) has been reported in rejection, severe acute tubular necrosis (ATN), renal vein obstruction, pyelonephritis, subcapsular hematoma *(Page kidney),* obstruction, and cyclosporine toxicity. The RI is also correlated with established cardiovascular risk factors.

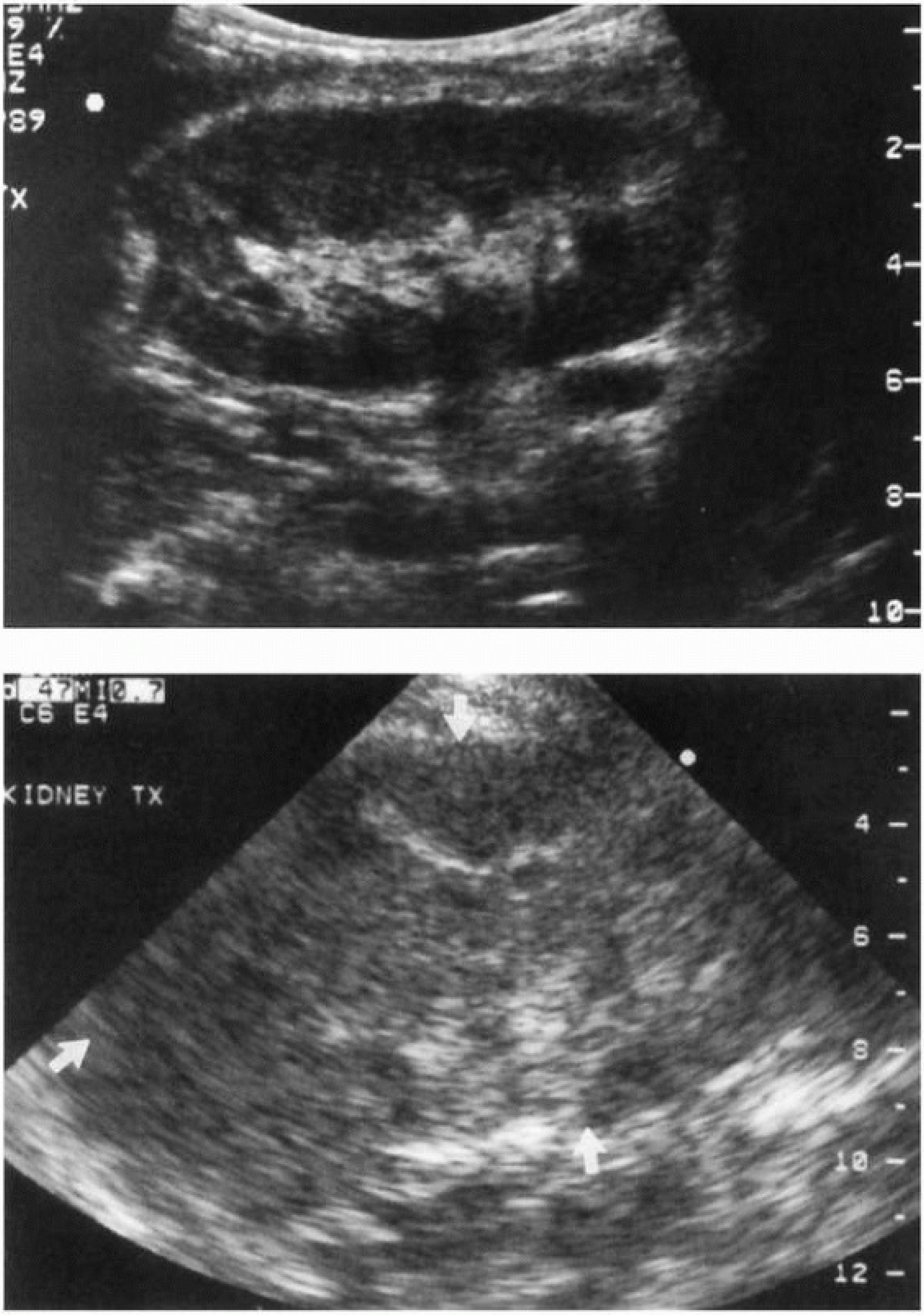
Although the renal transplant RI is nonspecific, it is a valuable predictor of long-term allograft performance. An RI of 0.8 or greater, measured 3 months after transplantation, has been reported to be associated with poor subsequent graft function.

Duplex Ultrasonography

Duplex US (or, more accurately, *triplex* if color, pulsed, and grayscale are employed simultaneously) combines a two-dimensional image with flow information, the latter being in the form of color, pulsed, and, most recently, power Doppler. These techniques employ the same sound waves as real-time imaging but measure the frequency and energy of the Doppler shift from the echoes interacting with flowing blood, allowing determination of flow presence, velocity, and direction (power Doppler does not assess the latter two). Color Doppler US provides an estimate of the mean velocity and direction of flow within a vessel by color-coding the information and displaying it superimposed on the grayscale image. Power Doppler (also known as *amplitude* or

energy map) measures the power of the Doppler signal and displays a greater range of signal strengths, thus allowing improved sensitivity to flow and visualization of smaller vessels. Power Doppler is displayed as a single color map of flow superimposed on a grayscale image but does not provide directional or velocity information as does color Doppler. Pulsed Doppler allows a sampling volume to be positioned in a vessel visualized on the grayscale image and provides a spectrum, or graph, of velocities of blood within the gate plotted as a function of time. A read-out of absolute velocities and calculation of the RI and PI are obtained using a spectrum from pulsed Doppler. Because the Doppler equation

uses the angle between the beam axis and the vessel to calculate the velocity (performed by the machine software), and this angle is estimated by the ultrasonographer, incorrect angle correction may yield spurious velocities.



A

B

FIGURE 13.5 A: Sonogram of normal transplant kidney. **B:** Sonogram of transplant undergoing rejection reveals graft enlargement, decreased echogenicity of renal sinus (compare to echogenic sinus in A) and obscured corticomedullary delineations. Margins of graft are marked by *arrows*.

NUCLEAR MEDICINE IMAGING OF GRAFT FUNCTION AND DYSFUNCTION

NM imaging is noninvasive and does not jeopardize renal function. The widespread use of sophisticated US techniques, however, has reduced reliance on NM in the post-transplantation period. Two types of radiopharmaceuticals are used for the evaluation of renal transplant function, based on their clearance from the plasma either by glomerular filtration or by tubular secretion. Table 13.1 provides an overview. Currently, the most frequently used radiopharmaceutical is ^{99m}Tc-mercaptotriglycine (MAG3). Of the older agents, ^{99m}Tc-DTPA is still a viable alternative. Iodine-labeled tracers are not ideal for imaging because the ^{123}I-labeled tracers are not standard in the United States. ^{131}I as a label is not preferred because the β emission causes a significant radiation dose, severely limiting the dose that can be administered. Evaluation of transplant flow and perfusion is not possible with ^{131}I radiopharmaceuticals.

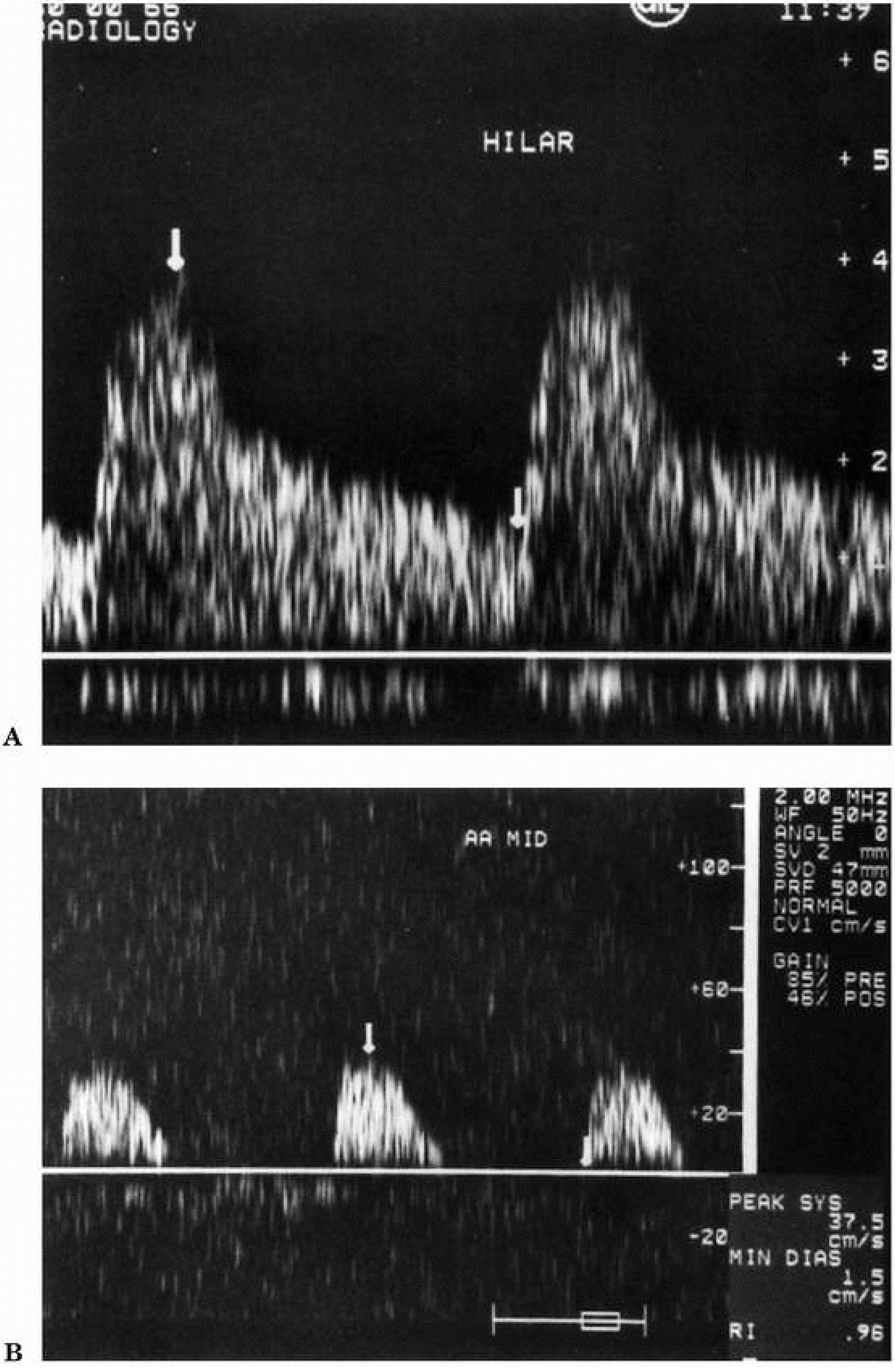


FIGURE 13.6 A: Normal pulsed-gate Doppler spectrum from kidney transplant with considerable flow throughout diastole and normal resistive index (RI = 0.65). **B:** Doppler spectrum of graft undergoing acute rejection with no diastolic flow (RI = 1). This is a nonspecific indicator of graft dysfunction.

The NM study most often applied is dynamic nephroscintigraphy (or NM renography), in which three phases are distinguished. The first phase assesses the flow and perfusion of the transplant and is known as the *angiographic phase*. The second phase reflects the concentration of tracer in the renal cortex, the *parenchymal phase*. The third phase is the *excretory phase*, reflecting the clearance of tracer, which permits an assessment of the integrity of the ureteral system. A time-activity curve is generated, depicting the activity in the transplant kidney in function of time. Because dynamic NM renography is a planar imaging technique, the measured counts from the kidney suffer from attenuation by tissues between kidney and camera, and from activity contributed by nonkidney tissue within the kidney region. After proper correction, a curve is generated corresponding to the renogram of the transplant. The NM images of a normal functioning transplant are shown in Figure 13.7A and the corresponding regions and curves in Figure 13.7B.

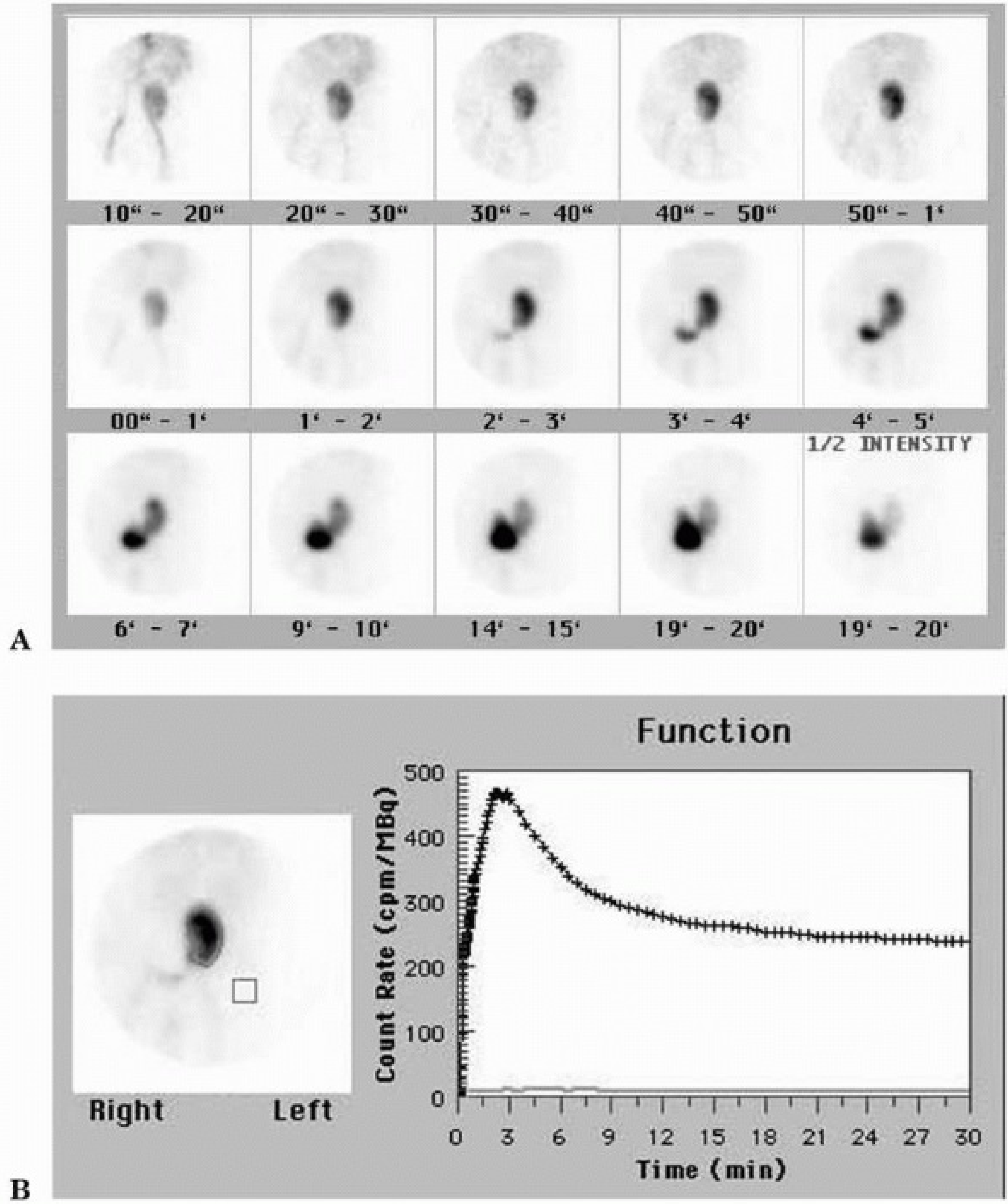


FIGURE 13.7 A: Dynamic images of a normal functioning transplant. The *top row* shows flow-perfusion images, each of 10 seconds' duration. The *middle* and *bottom rows* are 1-minute images taken during the subsequent 20 minutes. B: Regions of interest are drawn around the kidney and background *(box)* and curves generated of the activity within that region as function of time.

Acute Rejection

Typically, acute transplant rejection appears on dynamic NM renography as decreased

perfusion, delayed transplant visualization, poor parenchymal uptake, and high background activity because of decreased clearance (Fig. 13.8). Transplant rejection may also be detected by static imaging techniques. Increased uptake can be seen with ^{67}Ga-citrate, ^{99m}Tc -sulfur colloid, or ^{111}In-labeled blood components. Unfortunately, the low specificity of uptake of these latter agents prevents them from being of much value in the differential diagnosis of graft dysfunction, and they are considered obsolete for detecting rejection.

Despite the availability of various types of radiopharmaceuticals and the advancement of image technology, the differentiation between rejection and calcineurin inhibitor nephrotoxicity remains problematic. Attempts to use the renal cortical imaging tracer dimercaptosuccinic acid (DMSA) for this purpose have been unsuccessful.

Acute Tubular Necrosis

ATN typically shows good renal perfusion on the first-phase images, with preserved concentration during the second phase by the transplant. The third phase shows no excretion of tracer into the collecting system and bladder (Fig. 13.9). In addition, high surrounding tissue background activity is seen because of poor overall plasma clearance of the radiopharmaceutical. The renogram has the typical rising branch that reaches a plateau after 3 to 6 minutes. There is no descending branch because there is no excretion. These findings are

consistent with the pathophysiology of ATN, in which renal blood flow is preserved relative to glomerular filtration.

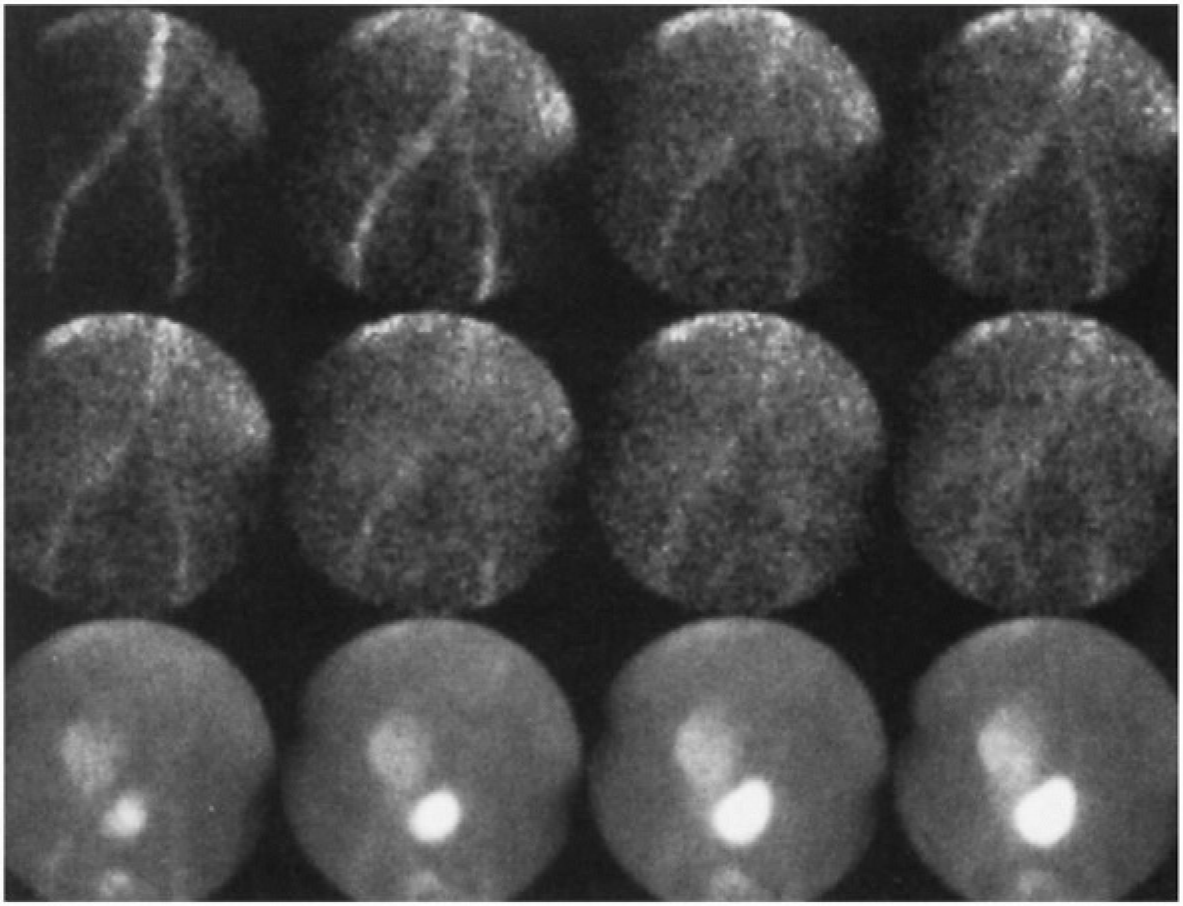


FIGURE 13.8 Nuclear medicine images of a transplanted kidney in rejection (radiopharmaceutical:^{99m} Tc mercaptotriglycine [MAG3]). Note the poor perfusion to the transplant, that is, delayed renal visualization in the initial images of the *top two rows* (5 seconds per image). The *bottom row* shows poor function (4 minutes per image). Overall, reduced function is represented by high surrounding background tissue activity, poor parenchymal washout of accumulated tracer, and reduced collecting system or urinary bladder activity.

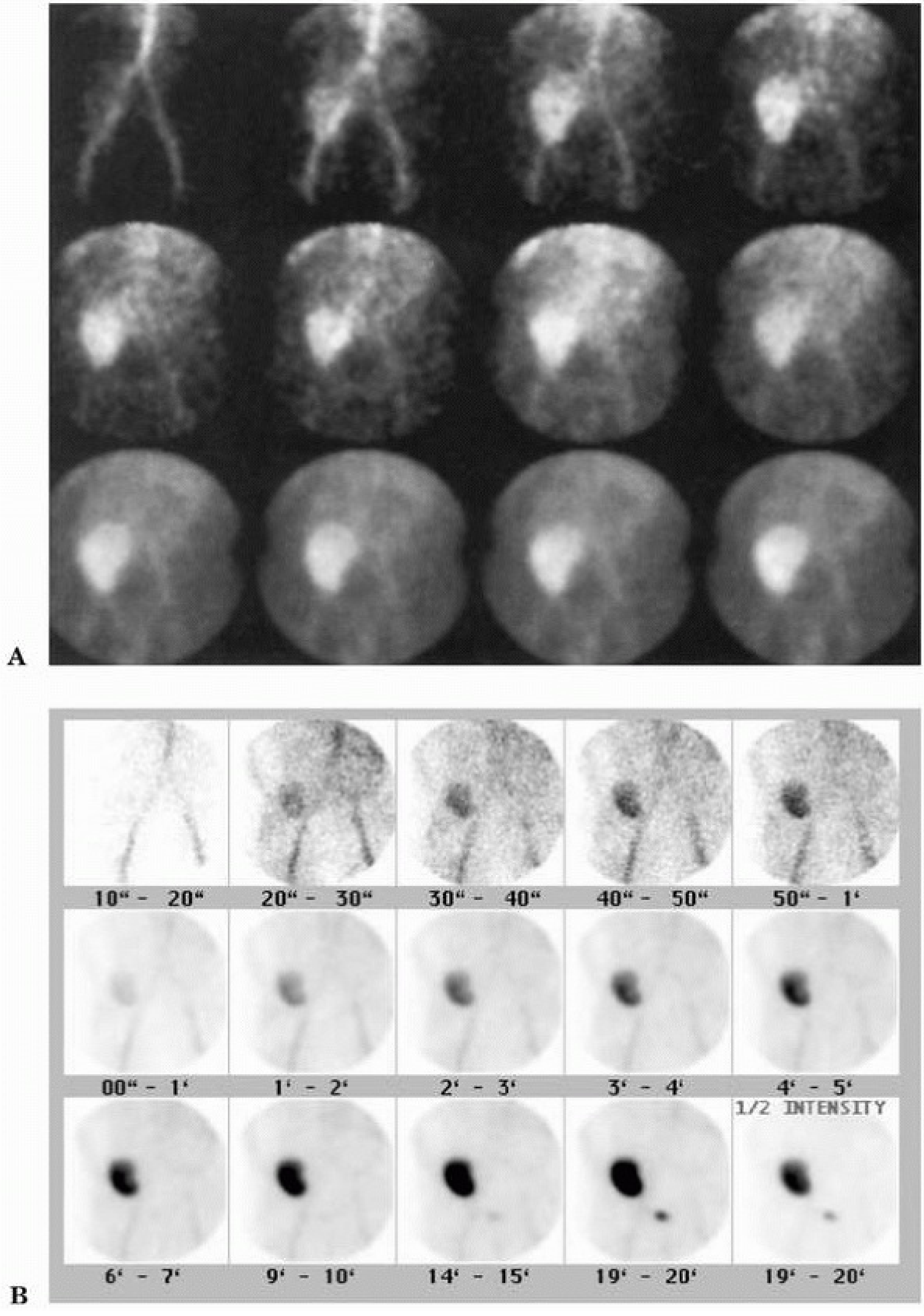


FIGURE 13.9 A: Nuclear medicine images of acute tubular necrosis. Note the wellpreserved perfusion in the transplant, that is, prompt renal visualization in the initial six images. Concentration of tracer by the transplant is maintained, but there is no excretion and no collecting system or urinary bladder activity. Radiopharmaceutical: ^{99m}Tc diethylenetriamine pentaacetic acid (DTPA). B: Study

performed with ^{99m}Tc mercaptotriglycine (MAG3) as radiopharmaceutical. *Top row* is the flow-perfusion phase (10 seconds per image). *Middle and bottom rows* show 1-minute images with normal renal concentration. There is visualization of tracer in the bladder in the last two frames, indicative of minimal function. Note the superior quality of ^{99m}Tc MAG3 over ^{99m}Tc DTPA in panel A.

Measurement of Glomerular Filtration Rate

Clinicians generally rely on the serum creatinine level as a marker of graft function, and although this simple test is indisputably invaluable in transplant management, its accuracy as a marker of glomerular filtration rate (GFR) is inconsistent. In chronic renal failure with proteinuria, tubular secretion of creatinine may form a significant percentage of total creatinine excretion and overestimation of GFR results. Radiolabeled DTPA, ethylenediaminetetraacetic acid (EDTA), and iothalamate (GLOFIL-125) are all accurate filtration markers that, like inulin, reach the urine by filtration without tubular secretion or reabsorption. The clearances of these compounds are equivalent to the classic inulin clearance. They are more convenient to use than inulin because their plasma and urine levels can be measured with a scintillation counter.

Absolute renal function can be measured with true clearance techniques. After bladder emptying, the radiopharmaceutical is administered intravenously, and serial blood and urine samples are taken over several hours. From the obtained curve, the rate of tracer disappearance from blood and concentration in urine is determined, from which the GFR is calculated with the standard clearance formula. GFR can also be assessed with this plasma tracer disappearance curve, by measuring rate and extrapolating the volume of distribution, the so-called plasma clearance. One- and two-sample methods have been developed for routine clinical use (Table 13.1).

POST-TRANSPLANTATION VASCULAR COMPLICATIONS

Arterial Thrombosis

Renal arterial thrombosis is an uncommon complication of transplantation and usually occurs in the early postoperative period. The most common causes are faulty surgical anastomoses, a thrombogenic state, severe acute rejection, and progression of a stenosis to thrombosis. The findings in color and pulsed Doppler imaging consist of absent arterial and venous blood flow within the graft. There is some controversy regarding the necessity of further imaging to confirm this diagnosis because there are several reported cases in which no flow was demonstrated by Doppler, but digital subtraction angiography revealed patent vessels. Power Doppler should, in theory, reduce false-positive results, but this remains to be proved because of interference from motion artifacts.

The dynamic NM images show lack of perfusion, absent visualization of the transplanted kidney, poor background clearance of activity, and sometimes a photopenic space in the transplant bed (Fig. 13.10). Renal vein thrombosis, acute cortical necrosis, and hyperacute rejection may all have similar scintigraphic findings.

Infarction

Acute segmental infarction may be diagnosed with Doppler US by demonstration of lack of flow to the infarcted region of parenchyma (Fig. 13.11). This diagnosis is facilitated by use of color and power Doppler, which both provide a global evaluation of flow to the organ, and help to identify segmental arteries, which can then be interrogated individually with pulsed Doppler.

Segmental renal infarction on NM scan (Table 13-1 lists the applicable radiopharmaceuticals) appears as a wedge-shaped, “cold” defect. DMSA is a radiopharmaceutical of the tubular secretion type, with a high uptake in the renal cortex (about 40%). This allows visualization of the mass of functioning renal tissue. Infarcts and scars appear as photopenic defects, demonstrating absence of functioning renal cells.

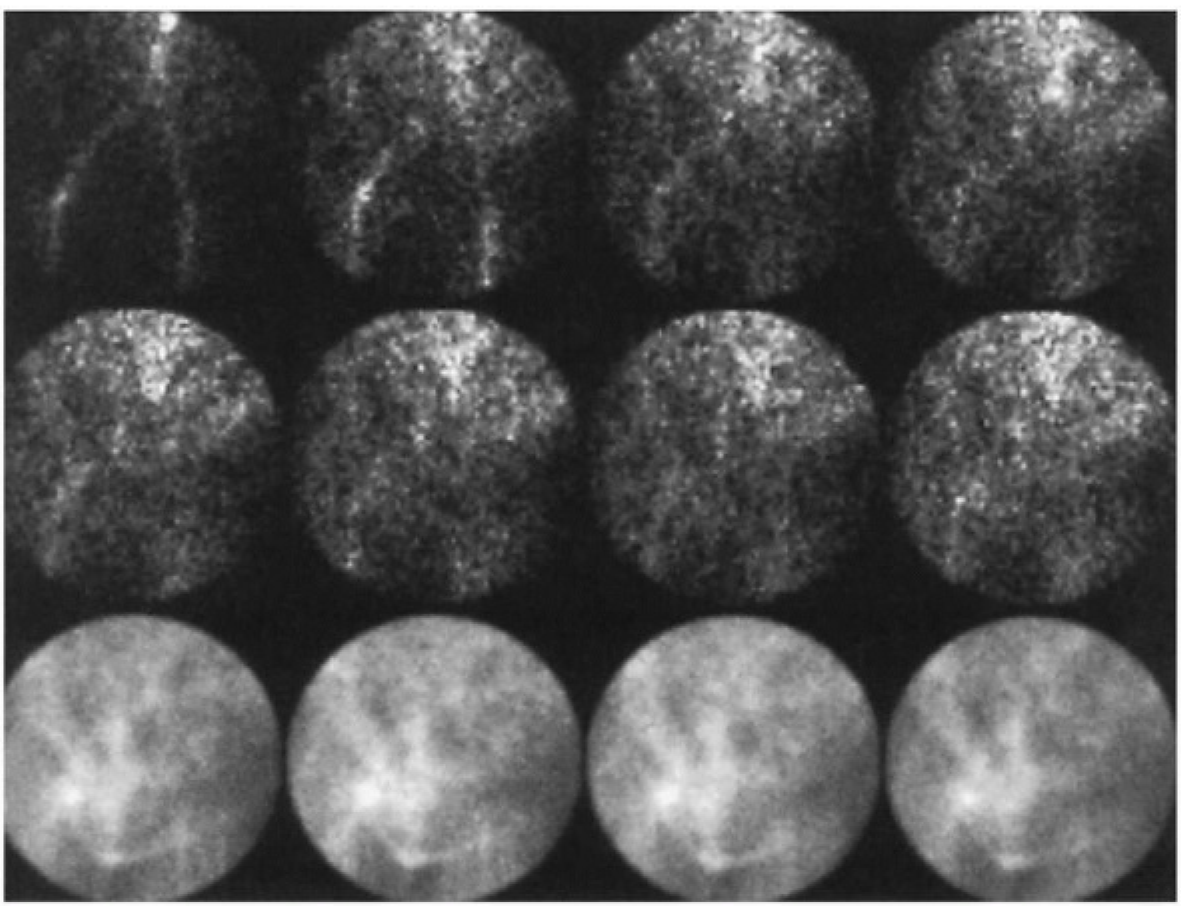


FIGURE 13.10 Nuclear medicine images of a transplanted kidney with renal artery thrombosis. Note the absence of renal perfusion, that is, nonvisualization of the

transplant in the *top two rows*. In addition, there is no activity in the collecting system and bladder. Background tissue activity remains high, indicative of absent excretion. Radiopharmaceutical: ^{99m}Tc diethylenetriamine pentaacetic acid (DTPA).

FIGURE 13.11 Color Doppler image reveals flow to most of the kidney, with absence of flow to area in upper pole, compatible with hypoperfusion and possible ischemia.

Renal Vein Thrombosis

Renal vein thrombosis is an uncommon complication that usually occurs in the first postoperative week. The US diagnosis is mainly dependent on the Doppler portion of the examination because the grayscale diagnosis is limited by the difficulty of direct visualization of the anechoic or hypoechoic acute thrombus and the nonspecificity of the frequently associated graft swelling and hypoechogenicity. The combination of

Doppler findings of high-impedance renal arterial waveforms with reversed, prolonged diastolic flow, a spikelike systolic component, and no detectable venous flow in the graft is highly suggestive of renal vein thrombosis (Fig. 13.12). Reversal of diastolic flow is a nonspecific finding that is reflective of increased arterial impedance in the graft. It may also be seen in ATN, acute rejection, and severe obstruction.

Chronic Rejection

In chronic rejection, there is gradual deterioration of kidney function, and the allograft is usually decreased in size. Angiographic findings include decreased blood flow and reduction of the number of arteries, which may be narrow and irregular. The nephrogram is patchy. US findings include decreased size of kidney, cortical thinning, and altered cortical echogenicity, often with increased echogenicity. Doppler US may show a nonspecific elevation in RI. NM images show reduced perfusion, shift of the renogram peak to the right, and decreased excretion.

Renal Artery Stenosis

Renal NM angiography may be useful in the diagnosis of renal artery stenosis (RAS) in a native kidney because the contralateral kidney acts as a control for comparison. In the transplanted kidney with RAS, there may be a delayed blushon scanning, but in the absence of a paired kidney, this finding is too nonspecific to be diagnostically reliable.

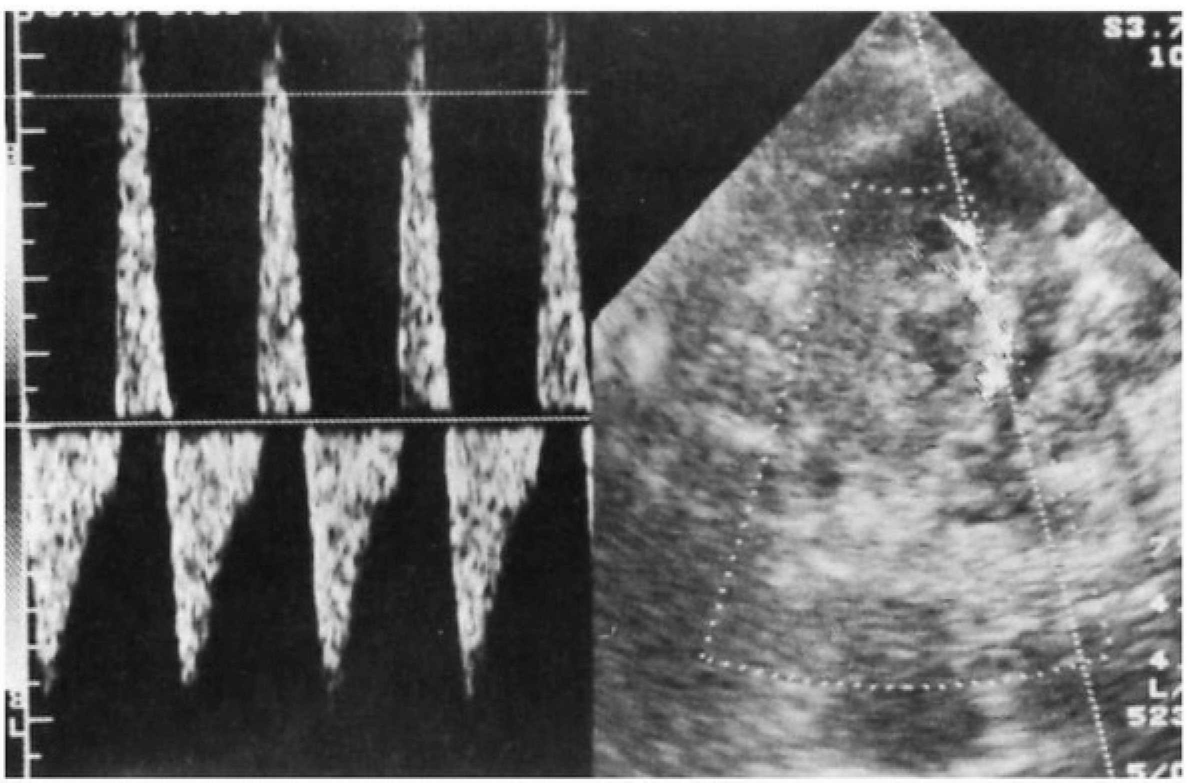


FIGURE 13.12 Duplex sonogram of transplant renal vein thrombosis demonstrates reversed flow in diastole and a spikelike systolic peak. No venous flow was

detectable in the kidney, renal hilum, or location of the renal vein.

The diagnosis of RAS by Doppler US is made by demonstration of a focal, segmental region of flow abnormality, characterized by elevated PSV and turbulent flow (Fig. 13.13). Various threshold values for PSV have been proposed for optimal detection of RAS, ranging from 100 to 300 cm per second; reported sensitivities and specificities range from fair to excellent. Because the normal range of PSV in the transplant renal artery may be variable, a ratio of PSV in the renal artery compared with the external iliac artery may be more useful. The accurate calculation of velocity by the machine's software, however, is highly dependent on the accuracy of the operator's estimate of the angle of insonation, and errors in this regard can yield spuriously elevated velocities. The accuracy of this estimate *(angle correction)* is dependent on the adequacy of delineation of the course of the renal artery, which is often small and tortuous. Color and power Doppler, by providing a map of the vascular anatomy, are helpful in tracing a vessel and therefore in determining the appropriate angle. A confident diagnosis of RAS using Doppler US can be made if the characteristic findings occur in a well-delineated vessel, allowing accurate angle correction. Conversely, high velocities without associated turbulence in a region where the accuracy of angle correction is equivocal must be viewed with skepticism.

Angiography remains the gold standard for diagnosis of RAS, and the threshold for performance of this study remains a matter of clinical judgment (see Chapters 9 and 10). CO_2 angiography provides a useful alternative to nephrotoxic iodinated contrast agents, but it may be less reliable than standard angiography.

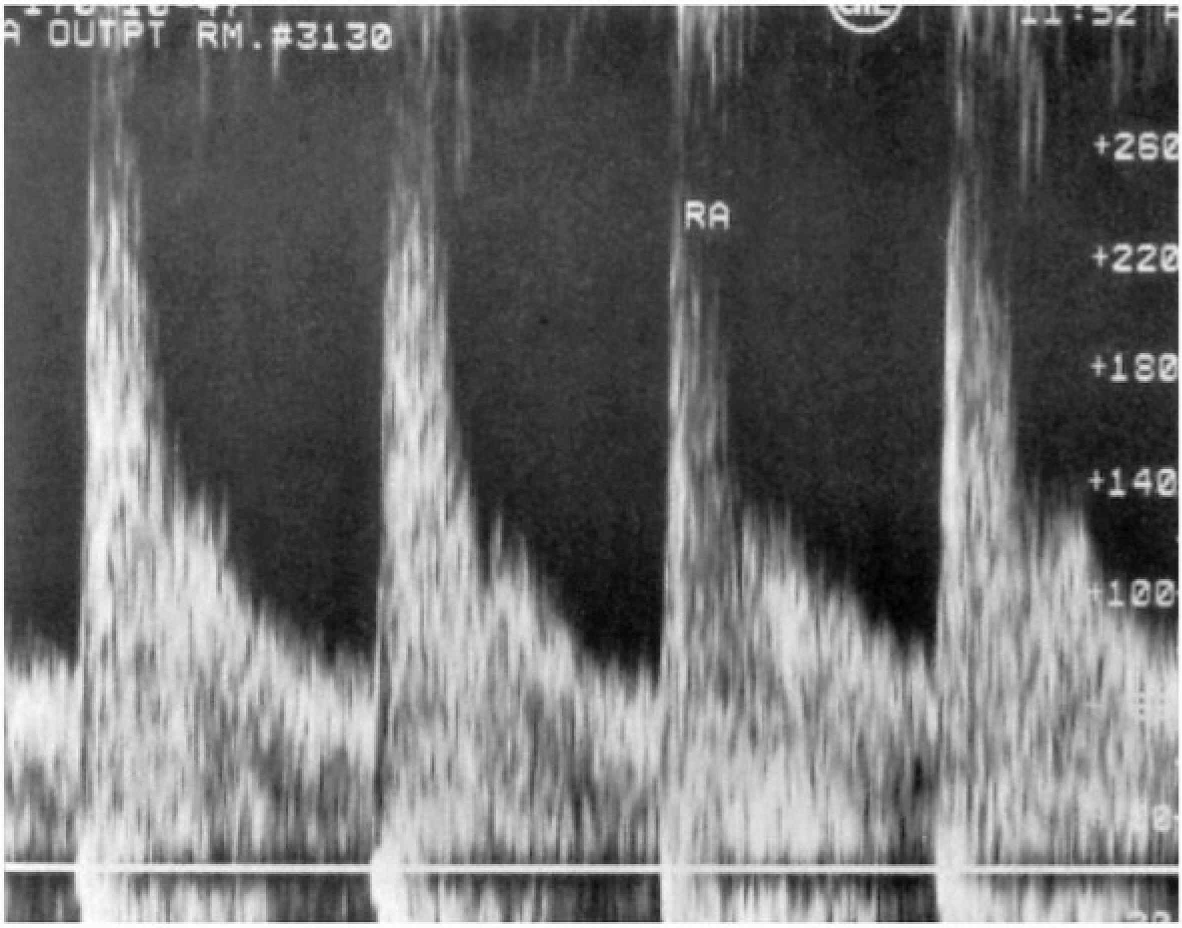


FIGURE 13.13 Renal artery stenosis. Doppler spectrum demonstrates focal elevated peak systolic velocity (faster than 260 cm per second), with mild spectral broadening at the anastomosis.

Arteriovenous Fistulas

Postbiopsy arteriovenous fistulas most often resolve spontaneously but can produce persistent hematuria or hypertension. Grayscale US cannot identify these small vascular communications, but they are readily demonstrated on color Doppler as an area of artifactual color assignment in the renal parenchyma (Plate 13.2). This finding is believed to be caused by high-velocity flow in the fistula, which results in localized turbulence and vessel wall vibrations that are transmitted to the perivascular tissues. The vibrating interfaces in the perivascular tissue produce phase shifts in the reflected sound wave and result in random color assignment in this region. This phenomenon is essentially the Doppler equivalent of a bruit.

After an area of suspicion is identified, the fistulized vessels may be visualized on color Doppler by virtue of their high-velocity flow. Confirmation of the presence of an arteriovenous fistula is achieved by performing waveform analysis with pulsed Doppler and by demonstrating high-velocity, low-resistance flow in the supplying artery, and

arterialization (highly pulsatile flow) of the waveform in the draining vein. A focal, intrarenal arterial stenosis can produce high-velocity flow and tissue vibration, thereby mimicking a fistula, but no changes in the venous waveform should occur.

Doppler US is readily able to demonstrate many fistulas and should be the initial, primary imaging modality. If no fistula can be demonstrated by US in a patient with persistent gross hematuria and hypertension, angiography may be necessary. Angiography is the examination of choice for defining the extent of the fistula and for treatment planning. Superselective occlusion of the segmental or interlobar branches is possible using a variety of occlusive devices, including steel coils and detachable balloons. CT and MR angiography could play a role in the diagnosis of a fistula but may be limited by spatial resolution issues.

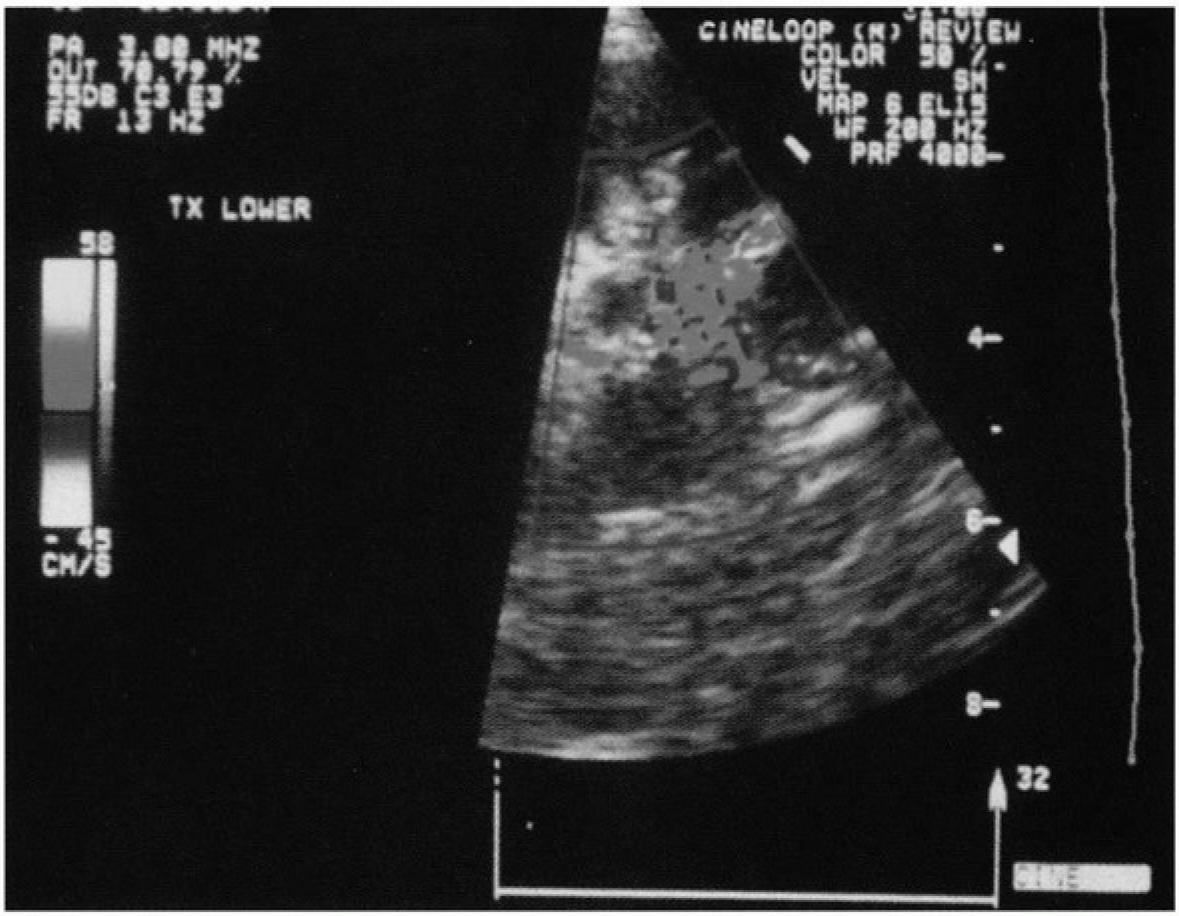


PLATE 13.2 Postbiopsy arteriovenous fistula. Color Doppler image shows an area of random color assignment. Pulsed-gate Doppler analysis revealed high-velocity, lowresistance arterial flow and arterialization of the venous waveform. see color image

Pseudoaneurysms

Pseudoaneurysms in a renal transplant may be intrarenal, usually secondary to a biopsy, or, less commonly, extrarenal, usually as a consequence of faulty surgical anastomosis or perianastomotic infection. Extrarenal pseudoaneurysms have a much higher risk for spontaneous rupture and are therefore treated as a relative surgical emergency. Arteriovenous fistulas may be associated with pseudoaneurysms. The US findings are the same for intrarenal and extrarenal pseudoaneurysms and consist of a spherical fluid collection that may or may not contain thrombus. Color Doppler reveals swirling internal flow (Plate 13.3) and occasionally adjacent tissue vibrations.

CONTRAINDICATIONS FOR CONTRASTED MAGNETIC RESONANCE IMAGING IN RENAL FAILURE PATIENTS

NSF is a relatively uncommon disorder linked to gadolinium-based contrast agents. The underlying pathology of the disorder is not clearly understood, but it is thought to be related to disassociation of the unexcreted gadolinium from the chelate in renally impaired patients. The excess gadolinium infiltrates multiple organs, inciting an inflammatory response that causes thickening of collagen bundles with increased number of fibrocytes. This process is typically bilateral and symmetrical and most commonly affects the skin of the distal extremities; the lower limbs are more commonly involved than the upper extremities. Although the skin is the most common site of involvement, the skeletal muscles, pleura, diaphragm, pericardium, and myocardium can also be affected. Fibrocyte and mucin infiltration leads to contractures, muscle weakness, and arthralgias. The symptoms appear 2 to 11 weeks after gadolinium exposure in up to 5% of patients at risk. The patients who are at most risk for acquiring this entity are those who are dialysis dependent or those with acute hepatorenal syndrome. NSF is extremely rare in patients with an estimated GFR of greater than 30ml/min.

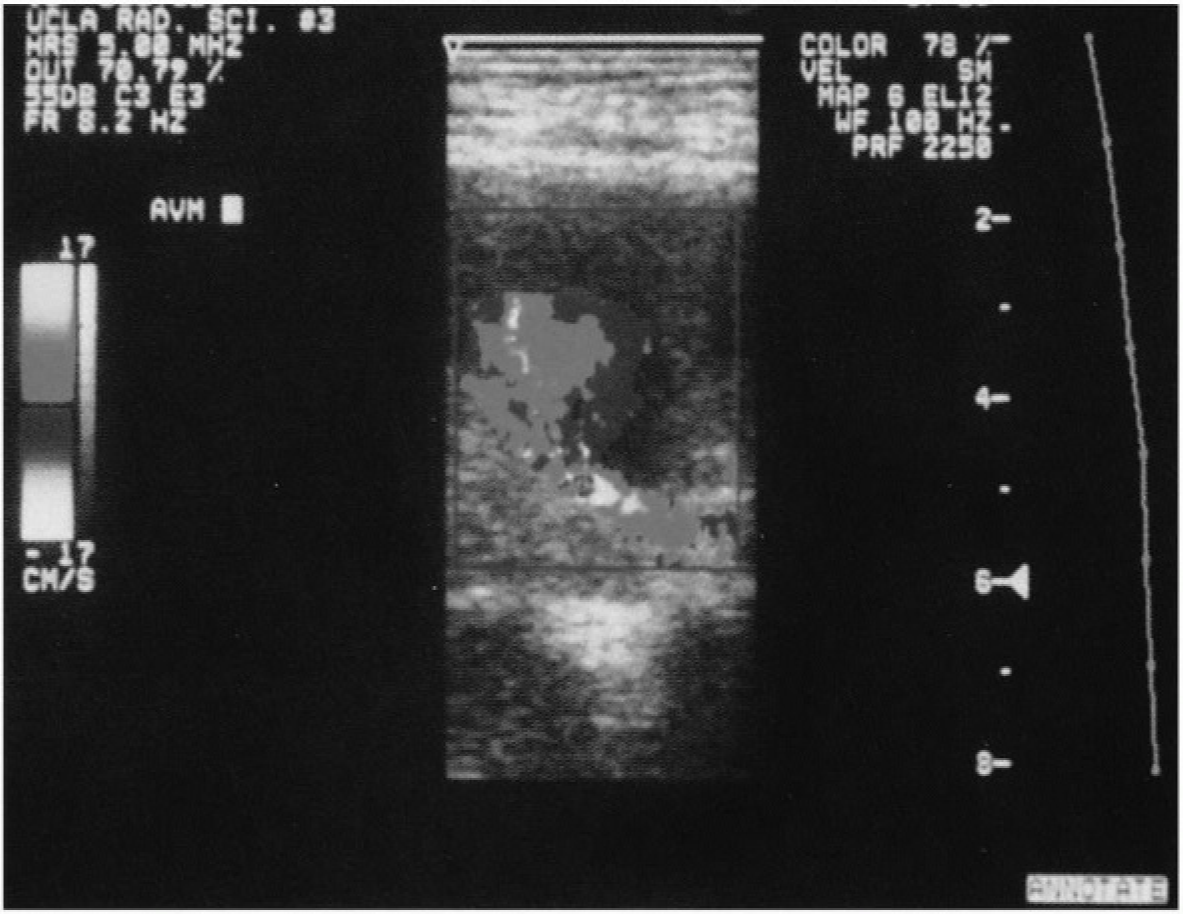


PLATE 13.3 Pseudoaneurysm. Grayscale image demonstrated a cystic lesion, and color Doppler image shows swirling internal flow. see color image

American College of Radiology Guidelines for Gadolinium-Based Contrast Use in Renal Impairment

- Gadolinium-containing contrast agents, especially at high doses (0.3 mmol/kg), should be used only if clearly necessary in patients with advanced kidney failure (those currently requiring dialysis or with a GFR of 30 mL/min or less), or patients with hepatorenal syndrome.
- Informed consent should be obtained.
- Gadodiamide (Omniscan) should not be used in contrast-enhanced MRI studies involving patients with any level of kidney disease. Although caution with the use of any of the five U.S. Food and Drug Administration-approved agents is recommended in moderate to severe renal failure.
- For patients already on hemodialysis, dialysis should be performed within 2 to 3 hours of administration of gadolinium-based intravenous contrast. A second hemodialysis should occur within 24 hours after gadolinium-based contrast administration.

Selected Readings

Broome D, Girguis M, Baron P, et al. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned AJR Am J Roentgenol 2007;188:586-592.

Brown E, Chen M, Wolfman NT, et al. Complications of renal transplantation: evaluation with US and radionuclide imaging. Radiographics 2000;20:607-622.

Bruno S, Ferrari S, Remuzzi G. Doppler ultrasonography in posttransplant renal artery stenosis: a reliable tool for assessing effectiveness of revascularization? Transplantation 2003;76:147-153.

Kay J, Bazari H, Avery L, et al. A 46-year-old woman with renal failure and stiffness of the joints and skin. N Engl J Med 2008;358:827-838.

Kanal E, Barkovich AJ, Bell C, et al. ACR Guidance document for safe MR practices: 2007. AJR Am J Roentgenol 2007;188:1-27.

Liam Y, Kock MC, Ijzermans JN, et al. Living renal donors: optimizing the imaging strategy- Decision- and cost-effectiveness analysis. Radiology 2003;226:53-62.

Martin L, Boris R. Interventional therapy of vascular complications following renal transplantation. Clin Transpl 2006;20:55-59.

Nakatani T, Uchida J, Han YS, et al. Renal allograft arteriovenous fistula and large pseudoaneurysm. Clin Transpl 2003;17:9-12.

Nankivell BJ, Cohn DA, Spicer ST, et al. Diagnosis of kidney transplant obstruction using MAG3 diuretic renography. Clin Transpl 2001;15:11-18.

Radermacher J, Mengel M, Ellis S, et al. The renal artery resistive index and renal allograft survival. N Engl J Med 2003;349:115-124.

Syed AA. Complications of renal transplantation. Radiographics 2005;25:1005-1356.

Tublin ME, Bude RO, Platt JF. The resistive index in renal Doppler sonography: where do we stand? AJR AM J Roentgenol 2003;180:885-892.

14

Pathology of Kidney Transplantation

Cynthia C. Nast

Arthur H. Cohen

The gold standard for assessing structural abnormalities in the transplanted kidney is standard tissue histopathology of a biopsy or transplant nephrectomy. Immunofluorescence also is necessary for identification of certain types of acute rejection, and electron microscopy may be required to evaluate glomerular lesions. Fine-needle aspiration with cytologic evaluation of cells aspirated from the graft using a thin needle has been used in the past to determine the cause of acute allograft dysfunction. However, the advent of thinner core needles with relative safety of the core biopsy procedure has minimized the use of aspiration cytology in the clinical setting.

CORE-NEEDLE BIOPSY

Indications and Technique

Kidney transplant biopsies are most frequently performed at times of graft dysfunction when the etiology cannot be accurately elucidated by clinical or noninvasive means. Protocol biopsies are performed at predetermined intervals after transplantation at some centers in an attempt to recognize so-called subclinical rejection (see Chapter 9); they also may be required as part of clinical trials for the evaluation of new immunosuppressive drugs (see Chapter 5). More precise clinical indications for biopsy are reviewed in Chapters 9 and 10. Transplantation programs vary in their reliance on biopsies and the clinical setting in which biopsies are performed.

Preparations for transplant biopsy are similar to those for biopsy of the native kidney. Informed consent is required from patients, who should be specifically warned of the risk for bleeding and occasional damage to the graft (see “Complications,” later). Before biopsy, coagulation studies are usually performed, although in the absence of liver disease, use of anticoagulants, thrombocytopenia, or a clinical history of bleeding, these may not be necessary. The blood pressure should be controlled at a level of less than 160/100 mm Hg.

The locations of the graft and biopsy site can be determined by palpation or by ultrasound guidance. A small pillow or towel rolled in the small of the patient's back may facilitate palpation. Ultrasound offers the advantage of more precise localization of the graft and its depth and may reduce the frequency of inadequate specimens. Ultrasound may detect perinephric fluid collections or hydronephrosis. It is unwise to perform biopsy through a fluid collection because of the inability to tamponade the biopsy site adequately. Significant hydronephrosis should be relieved before the biopsy is performed because it may be the cause of the graft dysfunction; a small blood clot after the biopsy may exaggerate the degree of obstruction. Generally, the upper or lower pole of the transplant is sought, depending on which is more easily palpated or is nearer the surface. If the location of the biopsy site is difficult to ascertain or if the kidney is deep, it is wise to use real-time ultrasound with visual guidance or a fixed biopsy guide device (see Chapter 13).

Disposable automatic spring-loaded needles (18-gauge needles are usually adequate) have largely replaced the traditional modified 14-gauge Vim-Silverman needle and may be less traumatic to the kidney. The site chosen for the biopsy is locally anesthetized with 1% lidocaine, and a small stab wound in the skin is made to facilitate the passage of the needle. Precise instructions for use of the newer needles are provided in the package inserts. The needles are advanced up to the depth determined by ultrasound or until an increase in resistance is felt as the needle makes contact with the kidney. When the automatic needles are used, it may be advisable to withdraw the needle slightly before taking the sample to avoid excessive depth and ensure a cortical sample.

Two biopsy cores should be adequate. It is advisable to inspect the specimen immediately with a stereomicroscope to ensure adequacy. As soon as the needle is withdrawn, hemostasis should be augmented by manual compression or with a sandbag. Postbiopsy orders should include observation of the patient's vital signs every 15 minutes for at least 2 hours and then hourly for several hours. Patients initially should be immobile; in the absence of macroscopic hematuria, ambulation can begin after 6 to 8 hours. Many transplantation centers permit outpatients to go home the same day the biopsy is performed.

Complications

Core needle biopsy is an invasive technique and is not risk free; these risks must be weighed against the benefit gained from the information obtained from the procedure. Careful assessment of potential risks and benefits must precede every decision to subject a patient to a biopsy.

All major complications after needle biopsy manifest as perinephric or urinary bleeding. Transient macroscopic hematuria is common and is of little clinical significance. Macroscopic hematuria follows about 3% of biopsies and may prolong hospitalization or lead to blood transfusion or placement of a bladder catheter for clot drainage. Ureteral

obstruction occasionally occurs, requiring placement of a percutaneous nephrostomy; massive hemorrhage necessitating surgical exploration, graft nephrectomy, or angiographic embolization is rare. Postbiopsy arteriovenous fistulas sometimes may be detected by Doppler ultrasound and usually can be treated expectantly. Angiographic embolization may occasionally be required, and graft loss has been reported.

Specimen Handling

Detailed methods for handling tissue specimens are beyond the scope of this chapter. For all specimens, portions are obtained for each of the three traditional methods of evaluating renal parenchyma: light microscopy, immunofluorescence, and electron microscopy. For the initial biopsy, all methods should be used; for subsequent biopsies, electron microscopy is performed only if indicated. This approach allows the pathologist to obtain maximal diagnostic and prognostic information. In selected instances, rapid processing or frozen sections can be performed on the tissue placed in fixative for light microscopy when an immediate assessment of the changes in the graft is necessary for initiating or modifying therapy.

TRANSPLANT REJECTION

Traditionally, three major forms of rejection are recognized: hyperacute, acute, and chronic. Each has reasonably distinctive changes, although acute and chronic rejection may be present simultaneously, resulting in a mixture of histopathologic features. Table 14.1 lists the pathologic findings in the major lesions responsible for functional impairment of the graft.

TABLE 14.1 Histopathologic Findings in the Major Causes of Allograft Dysfunction

Type	Interstitium	Tubules	Glomeruli	Arteries
Acute T-cell mediated rejection	Edema, lymphocytes	Lymphocytes, cell degeneration	Capillary lymphocytes	Swollen endothelium, intimal lymphocytes, foam cells

Arterial acute antibody-mediated rejection	Hemorrhage, zonal infarction, PTC C4d	Necrosis	Neutrophils, thrombosis	Necrosis, neutrphils, thrombosis
Microvascular (C4d+) acute antibody-mediated rejection	PTC C4d ± PTC neutrophils, monocytes	± Necrosis	Neutrophils, monocytes	Normal
Acute tubular necrosis	Edema	Cell degeneration, necrosis, mitoses	Normal	Normal
Acute calcineurin inhibitor toxicity	Edema	Isometric vacuoles, cell degeneration	Normal	Normal
Chronic rejection	Fibrosis, lymphocytes	Atrophy, dropout	Chronic transplant glomerulopathy	Fibrosis, lymphocytes narrowed lumina
Chronic calcineurin inhibitor toxicity	“Striped” fibrosis	Atrophy	Ischemic collapse	Arteriolopath hyalinization

PTC, peritubular capillary.

Hyperacute Rejection

Hyperacute rejection is produced by preformed cytotoxic antibodies and is an infrequent event so long as the pretransplantation crossmatch is negative (see Chapters 3 and 7). It may manifest shortly after vascular anastomoses are established, or it may be delayed up to 3 days. It is characterized by rapid and widespread vascular thrombosis, predominantly affecting arteries, arterioles, and glomeruli, often with polymorphonuclear leukocytes incorporated in the thrombi. The kidney is usually cyanotic, slightly edematous, and flaccid, and urine production suddenly ceases or does not begin at all. If the kidney is not removed immediately, extensive cellular necrosis ensues, followed after 24 hours by numerous cortical and medullary infarcts. Immunofluorescence may disclose capillary and arterial wall immunoglobulin G (IgG) or IgM, C3, and fibrin, with fibrin also in the thrombi. Peritubular capillary C4d deposition occurs after 48 to 72 hours if the kidney remains viable during this time. Electron microscopy in the early lesions indicates degeneration and early necrosis of vascular endothelium.

Hyperacute rejection needs to be differentiated from other circumstances in which extensive vascular thrombi occur. The differential diagnosis includes physical perfusion-related injury to vascular endothelium and injury caused by cold-reacting IgM antibodies against blood cells. Both of these conditions rarely may manifest in the immediate post-transplantation period and may produce entrapment of leukocytes in thrombi. It is only in hyperacute rejection, however, that polymorphonuclear leukocytes are typically and regularly incorporated in the thrombi. Recurrent hemolytic uremic syndrome and a thrombotic microangiopathy associated with administration of the calcineurin inhibitors (discussed later under "Calcineurin Inhibitor Nephrotoxicity") are characterized by thrombi, usually without leukocytes, and are generally lateroccurring lesions.

Acute Rejection

When the term *acute rejection* is used, it typically refers to acute *cell-mediated* rejection. However, two distinct immunopathologic mechanisms are responsible for acute rejection: cell-mediated immunity and antibody-mediated (humoral) immunity. It is critical to differentiate the processes.

Cell-Mediated Acute Rejection

Cell-mediated acute rejection is the most common form of early rejection and has tubulointerstitial and vascular forms. Light microscopy and immunofluorescence microscopy with C4d immunostaining (see "Antibody-Mediated Acute Rejection and the C4d Stain") are the major procedures used in diagnosing these lesions and in all cases of graft dysfunction. At times, routine immunofluorescence and electron microscopic evaluation may be helpful for the differential diagnosis. In *tubulointerstitial cell-mediated acute rejection*, primary abnormalities are in the interstitium, which is diffusely edematous and infiltrated by numerous leukocytes, most of which are mature and transformed lymphocytes (CD4, CD8), with fewer monocytes and plasma cells (Fig. 14.1). Eosinophils are either absent or found focally in small numbers; polymorphonuclear leukocytes are not a regular feature. Peritubular capillaries are dilated and contain lymphocytes that may be seen migrating into the interstitium. A characteristic lesion, called *tubulitis*, occurs, whereby lymphocytes and monocytes extend into the walls and lumina of tubules, with associated degenerative changes of tubular epithelial cells. The cells and basement membranes of tubular walls may be damaged and discontinuous. When this lesion affects cast-containing distal tubules, cast matrix (Tamm-Horsfall protein) may be found in the interstitium and occasionally in peritubular capillaries and small veins. For tubulitis to have diagnostic significance, the inflammation should be documented in normal (nonatrophied) tubules. The significance of tubulitis solely in atrophied tubules is not known.

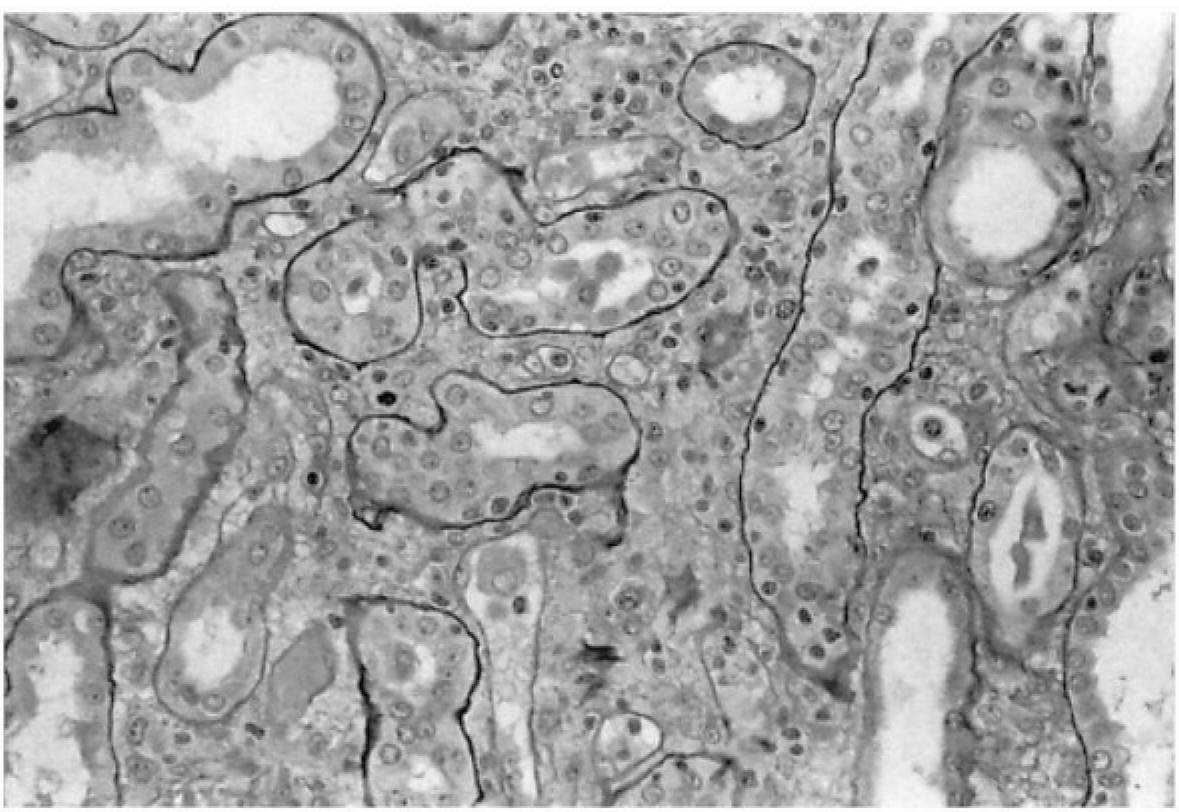


FIGURE 14.1 Acute cell-mediated tubulo-interstitial rejection. There is interstitial edema with lymphocytes in both the interstitium and tubular walls in association with tubular cell degeneration. (Periodic acid-methenamine silver stain, ×200.)

In *cell-mediated vascular rejection*, lymphocytes, monocytes, and less often foam cells undermine arterial endothelium and are found in the vascular intima, but rarely extend into the muscularis (Fig. 14.2). Endothelial cells are swollen, often vacuolated, and detached from the vacular wall, but arterial wall necrosis is not a feature of this type of acute rejection. This form of vascular rejection often occurs in concert with tubulointerstitial rejection. *Acute transplant glomerulopathy* is a form of glomerular cell-mediated rejection in which lymphocytes and monocytes accumulate in glomerular capillary lumina and mesangial regions (Fig. 14.3). Endothelial and mesangial cells are swollen, and capillary walls display subendothelial lucencies, with occasional segmental peripheral mesangial migration and interposition on ultrastructural examination. In biopsies demonstrating cellular rejection, immunofluorescence may disclose fibrin in the interstitium; segmental linear or granular IgM, C3, and fibrin may be found in glomerular capillary walls in acute transplant glomerulopathy. C4d staining is negative within peritubular capillaries. Ultrastructural examination usually confirms the light microscopic findings and provides additional diagnostic information only for the glomerular lesion. When acute cell-mediated rejection is treated successfully, the interstitial inflammatory infiltrate diminishes rapidly, whereas edema, tubular inflammation, and tubular cell damage may persist for some time.

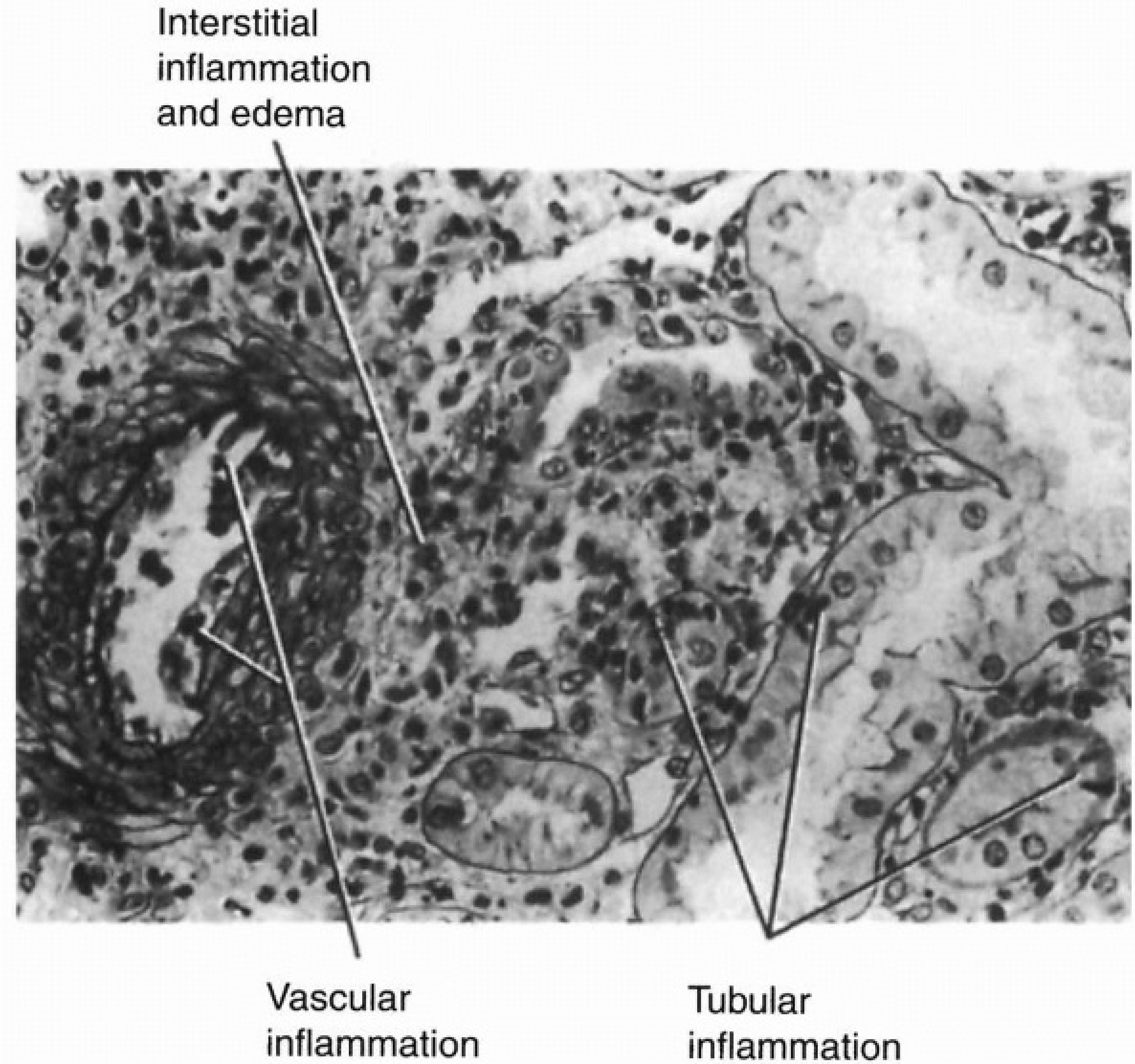


FIGURE 14.2 Acute cell-mediated vascular rejection. A small artery contains lymphocytes in the lumen and in the intima beneath swollen endothelial cells. Note the interstitial edema and infiltration by lymphocytes, which are also in the walls of tubules. (Periodic acid-Schiff stain, ×220.)

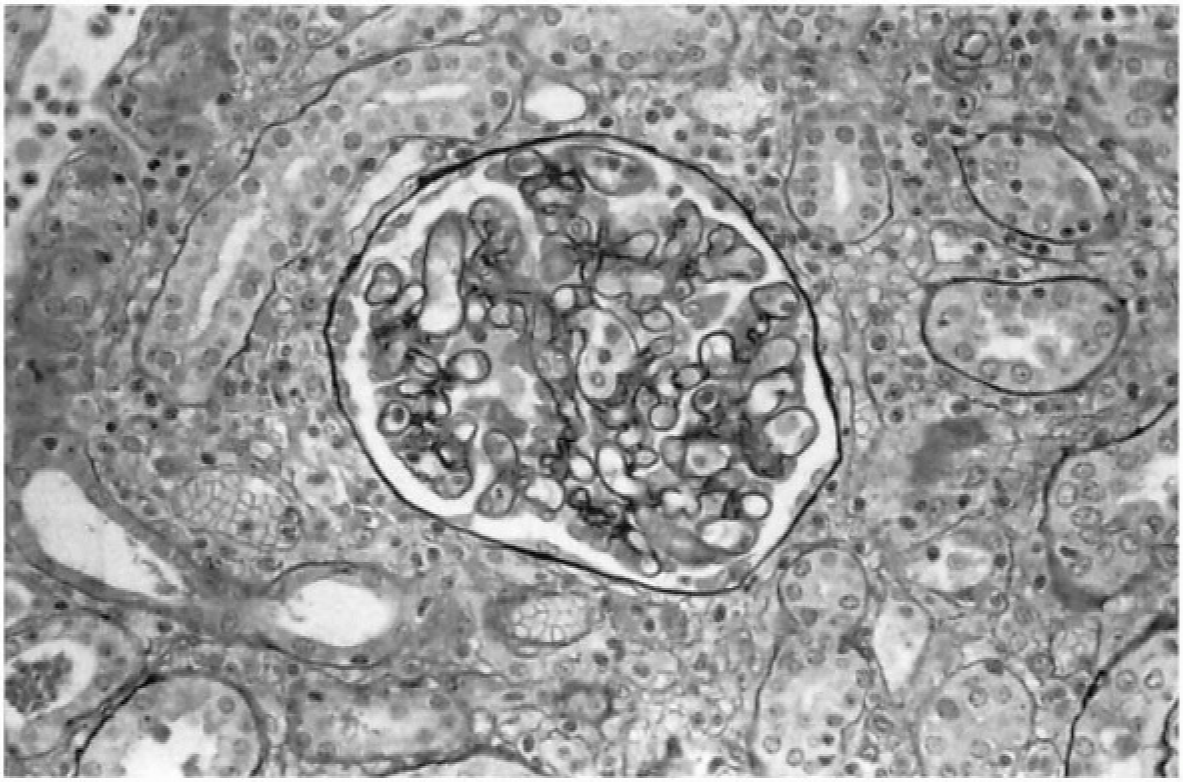


FIGURE 14.3 Acute transplant glomerulopathy. Glomerular capillary lumens contain monocytes and lymphocytes. There is also tubulo-interstitial rejection with interstitial edema, and lymphocytes in the interstitium and tubular walls. (Periodic acid-methenamine silver stain, ×200.)

Antibody-Mediated Acute Rejection and the C4d Stain

There are two types of antibody-mediated acute rejection: the classic arterial type and a more common type that is also C4d positive but without vascular involvement. The vascular form is an uncommon type of rejection and is characterized primarily by necrotizing arteritis, with mural fibrinoid necrosis and variable inflammation in the artery wall, including lymphocytes, monocytes, and neutrophils (Fig. 14.4). Endothelial cells are severely damaged or absent, and luminal thrombosis is common. This lesion typically results in cortical infarction with focal interstitial hemorrhage. Although the hyperacute rejection described previously is also antibody mediated, it differs from antibody-mediated vascular rejection in that it does not have an inflammatory or fibrinoid component in the vessel walls at its outset.

In the arterial form of antibody-mediated rejection, immunofluorescence discloses IgG and sometimes IgM accompanied by C3 in the walls of arteries. In these structures, fibrin may be intramural and intraluminal and also may be in the interstitium when hemorrhage is present. In cell-mediated vascular rejection, there is no antibody component; therefore, *vascular rejection* is an imprecise term that signifies merely

inflammation of arteries, which can result from either cell-mediated or antibody-mediated immunity. When arterial inflammation is present, it is important to further categorize the rejection process to indicate the etiologic mechanism because appropriate therapy and prognosis differ. The antibody-mediated form is characterized by arterial mural necrosis, neutrophilic infiltrate, and luminal thrombosis and represents a more severe lesion that is poorly responsive to therapy.

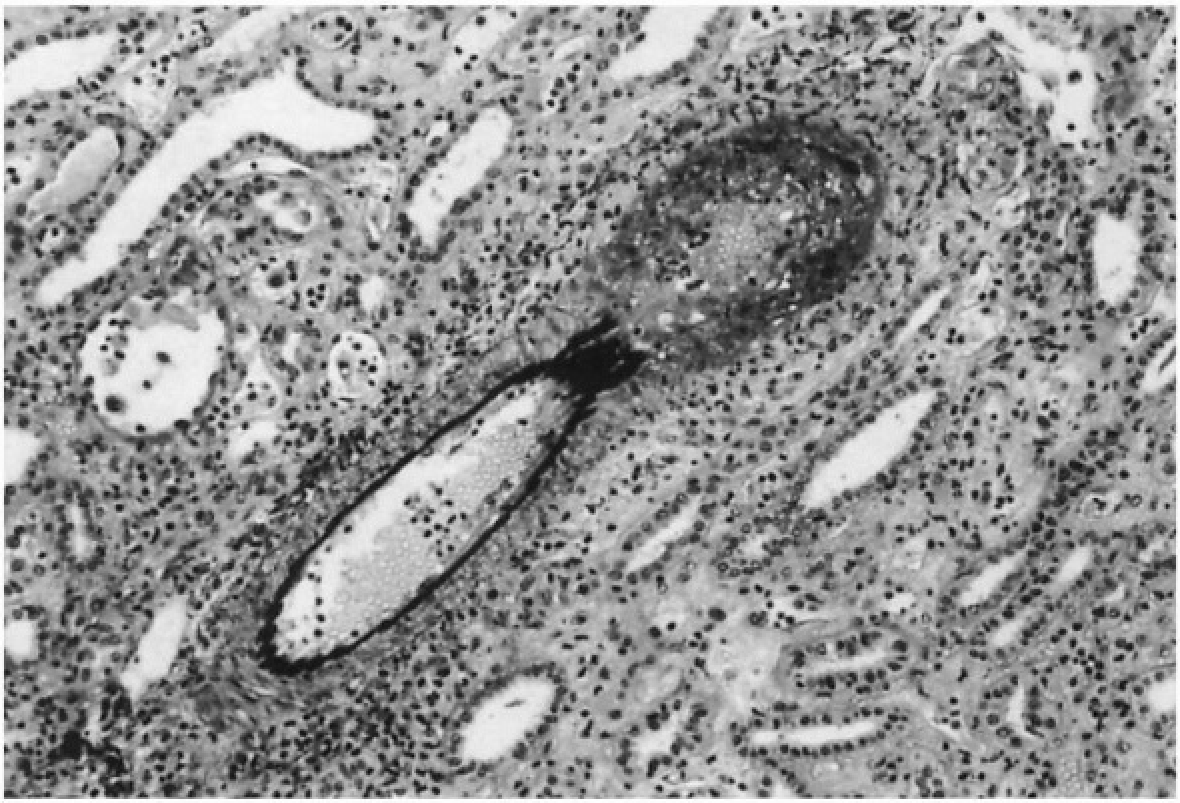


FIGURE 14.4 Antibody-mediated rejection, classic vascular type. The arterial wall is infiltrated by neutrophils and lymphocytes and has segmental fibrinoid necrosis. There are edema and inflammation in the adjacent interstitium. (Elastic-van Gieson stain, ×175.)

The more frequent form of antibody-mediated acute rejection is characterized by diffuse peritubular capillary staining for the complement component C4d. C4d was first associated with renal allograft rejection in the early 1990s and subsequently linked to the presence of donor-specific antibodies and humoral rejection. The recognition of the importance of the C4d stain has been a major step forward in the understanding of the role of antibodies in the rejection process. C4d has been described as a “footprint” for the presence of antibody-mediated rejection.

C4d is a split product of C4 involved in the classic complement cascade. Its formation is illustrated in Figure 14.5 and the accompanying legend. C4d is covalently bound to

peritubular capillary endothelium or basement membrane collagen and is a marker for the complement activation associated with humoral rejection (Fig. 14.6). The histologic appearance of this type of rejection is diverse. It may be associated with scattered glomerular, peritubular capillary, and tubulointerstitial neutrophils or monocyte-macrophages. It also may appear only as acute tubular necrosis or may accompany cell-mediated rejection. The only way to diagnose this antibody-mediated process is with immunostaining for C4d, which is most reliable in frozen-section specimens and should be performed on all biopsies obtained for renal transplant dysfunction. The treatment and prognosis for this type of rejection are different than for cell-mediated and classic vascular humoral rejection (see Chapters 5 and 9).

Differential Diagnosis of Acute Cell-Mediated Rejection

Other forms of acute interstitial nephritis may have many of the same structural lesions as acute rejection, including infectious interstitial nephritis (viral, bacterial) and drug-induced acute hypersensitivity interstitial nephritis. Certain viral and bacterial interstitial nephritides may be characterized by a mononuclear, rather than polymorphonuclear, infiltrate, thereby simulating rejection. Glomerular inflammation and arterial inflammation, when present, indicate rejection. Because of the negligible role of polymorphonuclear leukocytes in

acute cellular rejection, their presence should be taken to signify acute infection or C4d humoral rejection, especially when fresh infarction is excluded. Acute hypersensitivity lesions induced by drugs may have a prominent component of eosinophils and sometimes granulomas. Some biopsy specimens with calcineurin inhibitor toxicity may have focal interstitial lymphocytic perivenous infiltrates, but these are not associated with tubulitis or diffuse interstitial edema.

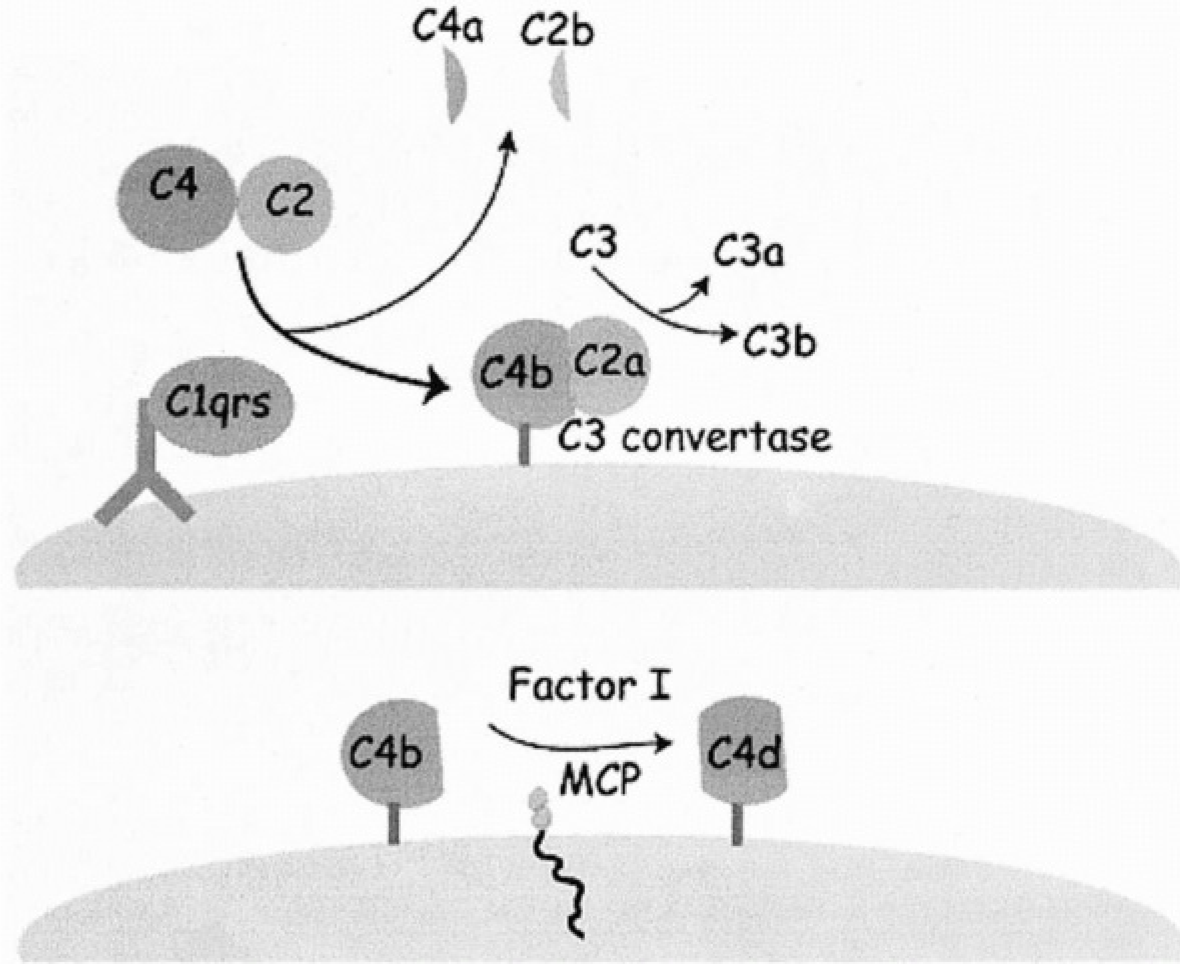


FIGURE 14.5 Complement activation and formation of C4d. **Top:** Binding of complement-fixing antibodies to a cell surface recruits C1qrs complexes. C1qrs cleaves and activates C4 and C2. C4b formed in this way may form covalent bonds with the cell surface and associate with C2a to form C4b2a, the classic complement pathway C3 convertase. C4b2a catalyzes cleavage of C3 and C5, amplifying complement activation. **Bottom:** C3 convertases are controlled by various mechanisms. One mechanism involves cleavage of C4b by factor I plus membrane co-factor protein (MCP) or C4-binding proteins as cofactors to yield C4d, which is catalytically inactive. Although C4d is catalytically inert, it can interact with C4d receptors on B cells and follicular dendritic cells. These interactions may help to regulate humoral immune responses. (From Platt JL. C4d and the fate of organ allografts. J Am Soc Nephrol 2002;13:2417-2419, with permission.)

Subclinical rejection describes a morphologic pattern of acute cell-mediated rejection that may occur in up to 30% of patients without clinical signs or symptoms of rejection or after apparently successful treatment of rejection. The significance of this asymptomatic inflammatory process relative to short-term or long-term renal function is discussed in Chapter 9.

Differential Diagnosis of Antibody-Mediated Rejection

The arterial inflammation in classic vascular antibody-mediated rejection may be indistinguishable from a systemic necrotizing arteritis, but recurrence of vasculitic lesions in the transplant is rare. The effects of vascular occlusion, infarction, and parenchymal hemorrhage may be manifestations not only of arteritis

but also of arterial occlusion from other causes, including surgical ligation of a large artery and emboli of any nature. The morphologic changes found in C4d humoral rejection may appear to mimic other lesions in the renal allograft and require immunostaining for identification of the C4d and accurate diagnosis.

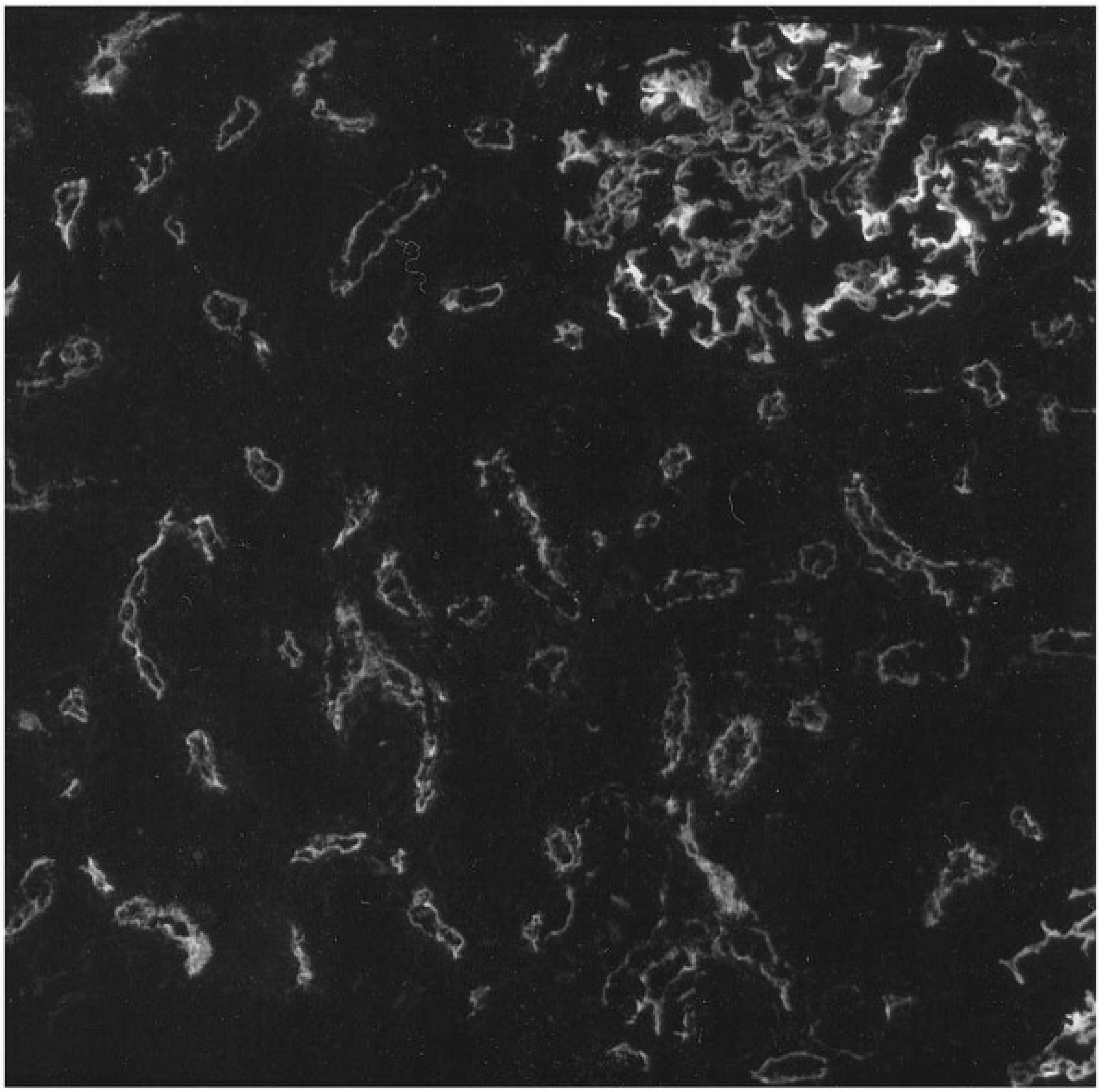


FIGURE 14.6 Acute microvascular antibody-mediated rejection. Peritubular capillaries stain diffusely for C4d. There is constitutive glomerular staining. (Immunofluorescence, ×200.)

Chronic Changes in the Allograft

Although the term *chronic allograft nephropathy* has been popular, it is nonspecific, lacks precision, is not well understood, and certainly does not indicate causality; consequently, it appropriately has fallen out of favor. Morphologically, chronic abnormalities include, but are not limited to, interstitial fibrosis and tubular atrophy (IFTA). These are features of many of the chronic processes which may affect the allograft and include chronic rejection, chronic calcineurin inhibitor toxicity, hypertension and nephrosclerosis, chronic obstruction, viral infections, recurrent diseases, and so forth. In many instances, it is possible to distinguish one process from the other by microscopic examination of kidney tissue (biopsy or nephrectomy); when distinguishing features are not present, use of the nonspecific but descriptive term *IFTA* is appropriate. Thus, *chronic allograft nephropathy* is no longer part of the vocabulary of transplant pathology. It is unfortunate that many studies dealing with therapy and prognostic indicators in the recent past have used it without reference to specific biopsy features to allow precise classification of the lesions, thereby obscuring potentially important data. In this section, the important entities responsible for chronic damage are described separately. Table 14.1 summarizes some of these. Table 14.2 addresses changes in the Banff classification related to chronic damage.

Chronic Rejection

The pathologic changes of chronic rejection are primarily cortical. There is patchy *interstitial fibrosis* with infiltrates of lymphocytes, plasma cells, and mast cells associated with *tubular atrophy* or tubular dropout. There may be neoexpression of the α_3 chain of type IV collagen and laminin B2 in the proximal tubular basement membrane and a significant increase in interstitial type I collagen. The walls of arteries are thickened with intimal fibrosis and sometimes with medial fibrosis, with variable mononuclear leukocyte inflammation (including foam cells) and with disruption and duplication of the internal elastic lamina, all resulting in luminal narrowing (Fig. 14.7). Immunofluorescence may document IgG, IgM, C3, and fibrin in the walls of arteries. In addition, juxtaglomerular apparatus hyperplasia may be present and is indicative of large artery involvement.

The glomeruli in chronic rejection are often, but not always, abnormal and exhibit a variety of changes, many of which constitute the lesion of *chronic transplant glomerulopathy,* which may occur as early as 4 months after transplantation (Fig. 14.7). This abnormality represents chronic glomerular rejection with the light microscopic changes of capillary wall thickening with a doublecontoured appearance. Mesangial matrix, mesangial cells, or both are increased, a process that may result in a lobular appearance. Segmental sclerosis frequently occurs. *Mesangiolysis,* or dissolution of mesangial matrix, occasionally is seen, with resulting capillary microaneurysms.

Immunofluorescence often discloses mesangial and capillary wall granular deposits of IgM, Clq, and C3, with linear fibrin along capillary walls. When segmental sclerosis also is present, IgM and complement are in capillary walls in a segmental distribution with a coarsely granular-to-amorphous pattern. Electron microscopy reveals a variety of abnormalities, including subendothelial new basement membrane formation, subendothelial flocculent material, infrequently subendothelial and mesangial electron-dense deposits, and peripheral migration of mesangium. Recently, it has been recognized that specific morphologic changes may be indicative of antibody-mediated chronic rejection. Patients with this process display slow progressive loss of graft function, often with proteinuria and hypertension. The diagnostic criteria for chronic antibody-mediated rejection overlap with those of the acute form in that both have positive peritubular capillary C4d staining, although it may be focal with additional glomerular capillary wall staining in chronic rejection. Features of chronic antibody-mediated rejection include *multilayering* of peritubular and glomerular capillary basement membranes; this change has been correlated with C4d deposition and likely represents the result of repetitive damage and repair of lining endothelial cells. Tubular atrophy and interstitial fibrosis also are found but are not specific unless accompanied by C4d staining and evidence of microvascular injury. Chronic antibody-mediated rejection has been associated with anti-HLA antibodies, specifically with those against major histocompatibility complex class II antigens. However, the long-term prognosis and therapy of this form of rejection are not known at this time.

TABLE 14.2 Selected Features of the Banff 1997 Classification with 2005 Update

Grade	Criteria
2. Antibody-mediated (humoral) rejection	
Acute rejection I	C4d+, acute tubular necrosis-like
Acute rejection II	C4d+, capillary polymorphonuclear leukocytes, and/or thrombosis

Acute rejection III	C4d+, transmural arteritis, fibrinoid necrosis
Chronic active rejection	C4d+, capillary double contours, peritubular capillary multilayers
3. Borderline changes (suspicious for cell-mediated rejection)	Tubulitis with insufficient interstitial inflammation (<25% of parenchyma)
4. T-cell-mediated rejection	
Acute rejection I	Interstitial inflammation (>25% of parenchyma)
	Moderate or severe tubulitis (>4 lymphocytes per tubular cross section)
Acute rejection II	Intimal arteritis (mild to severe)
Acute rejection III	Transmural arteritis and/or fibrinoid necrosis with lymphocytes
Chronic active rejection	Features of chronic and acute rejection

5. Interstitial fibrosis and tubular atrophy	No specific etiology
I	Mild interstitial fibrosis and tubular atrophy
II	Moderate interstitial fibrosis and tubular atrophy
III	Severe interstitial fibrosis and tubular atrophy or dropout
6. Other	Chronic changes not due to rejection; may occur with rejection

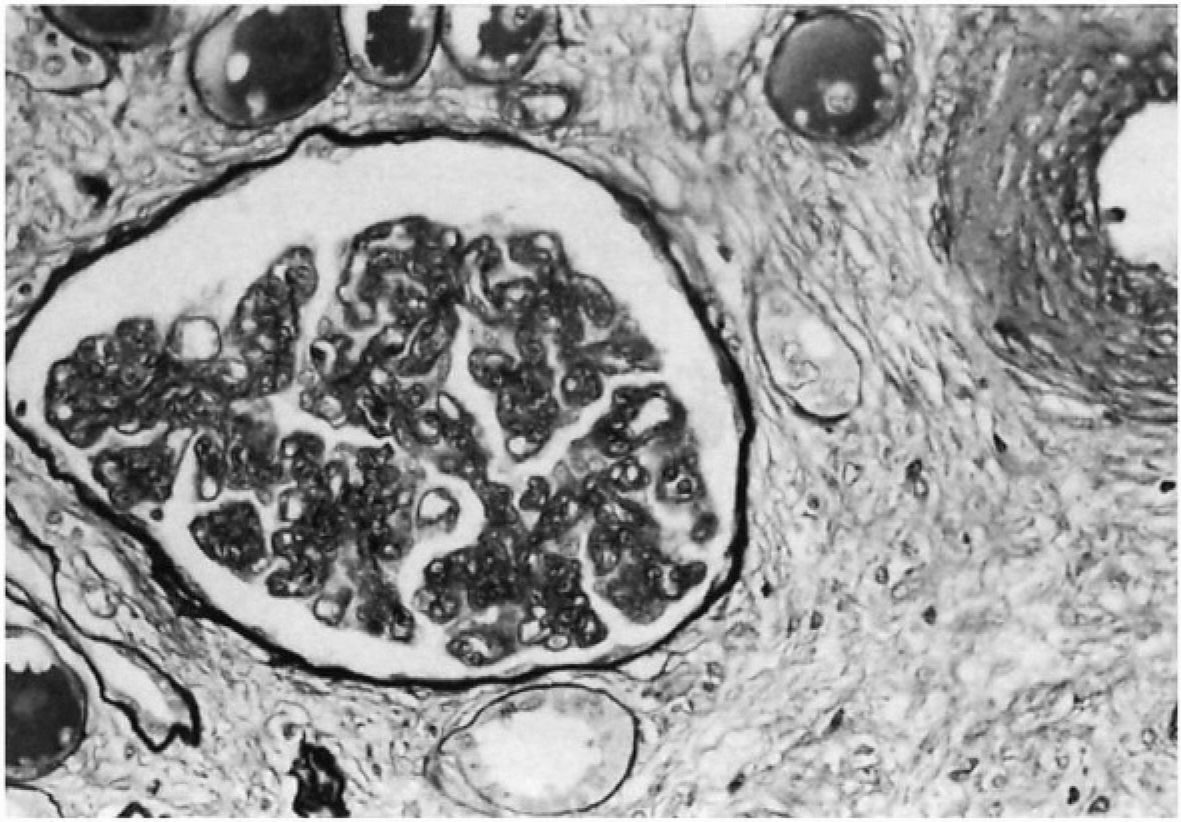


FIGURE 14.7 Chronic rejection with chronic transplant glomerulopathy. The arterial wall is thickened and the lumen narrowed as a result of intimal fibrosis. Glomerular capillary walls often display “double contours,” and monocytes are within widened mesangial regions and few capillary lumina. (Periodic acid-methenamine silver stain, ×200.)

As with other forms of chronic renal parenchymal diseases, acquired cystic disease has been documented in the chronically rejected transplant. In an attempt to provide prognostic information and standardization of the pathologic changes of chronic allograft failure, a *chronic allograft disease index* (CADI) was developed. Its use may permit prognostication and evaluation of therapeutic interventions for chronic allograft failure, although its reliability has not yet been fully validated.

Differential Diagnosis

As noted previously, these changes need to be differentiated from those of hypertension and chronic calcineurin inhibitor toxicity among other processes with interstitial fibrosis and tubular atrophy. The presence of transplant glomerulopathy, arterial fibrosis with or without inflammation, and exaggerated interstitial type I collagen is highly consistent with chronic rejection specifically. In the absence of these findings, other chronic lesions may be difficult to differentiate from chronic rejection.

Calcineurin Inhibitor Nephrotoxicity

Cyclosporine and tacrolimus produce similar renal structural and functional effects, and the pathologist cannot differentiate between the nephrotoxic affects of these two drugs. More recently, similar morphology has been described as a consequence of sirolimus administration. The pathogenesis of calcineurin inhibitor nephrotoxicity is discussed in Chapter 5.

Acute Toxicity

The structural abnormalities of acute calcineurin inhibitor toxicity are minimal; the dysfunction likely relates to calcineurin inhibitor-induced alterations in renal blood flow. Findings include tubular dilation, tubular cell flattening, and occasional individual tubular cell necrosis, all with little or no interstitial edema or inflammation. Giant mitochondria and focal tubular calcification also may be present. Unlike the lesions of acute rejection, lymphocytes, when present, are usually restricted to peritubular capillary lumens and small perivenous foci in the interstitium. They rarely are observed in tubules and are not in any other vascular location. Uniform, clear, small isometric vacuoles may be seen in a variable number of proximal tubular cells, often involving many cells of only few tubular profiles, but are not present in most biopsies from patients with toxicity (Fig. 14.8).

Vascular Effects

A number of structural lesions of the vasculature are ascribed to the calcineurin inhibitors. *Arteriolopathy* consists of a variety of abnormalities that occur separately or together. There is necrosis of individual myocytes, and the lost smooth muscle cells are replaced with large plasma protein precipitates; these insudates (hyalinization) are characteristically nodular, occurring on the outer aspect of arteriolar walls (Fig. 14.9). In contrast, in hypertension, the insudative lesions are more typically subendothelial or within the muscularis, although in diabetic patients, the same outer nodular hyalinization may be found. Cessation or reduction of the cyclosporine dose has resulted in amelioration or resolution of the arteriolopathy in some patients.

Thrombotic microangiopathy (TMA) is an idiosyncratic, uncommon, but well-recognized complication of calcineurin inhibitor administration and also has been associated with mTOR inhibitors; its clinical diagnosis and manifestations are discussed in Chapters 5 and 9. In its mildest form, bland thrombi are present within lumens of arterioles and glomerular capillaries. These lesions are rarely widespread or associated with extensive tissue necrosis. If severe and prolonged, however,

---

TMA may result in more severe arterial and arteriolar alterations with extensive cortical necrosis similar to that observed in full-blown TMA. In patients whose renal failure is caused by thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic

syndrome, it may be impossible to differentiate recurrent disease from calcineurin inhibitor-induced TMA. However, the pronounced intimal changes (“onionskin” lesions) of interlobular arteries seen in TTP are not regular features of the calcineurin inhibitor-associated process. Hepatitis C virus infection has been linked to anticardiolipin antibodies, which may induce TMA in allograft recipients.

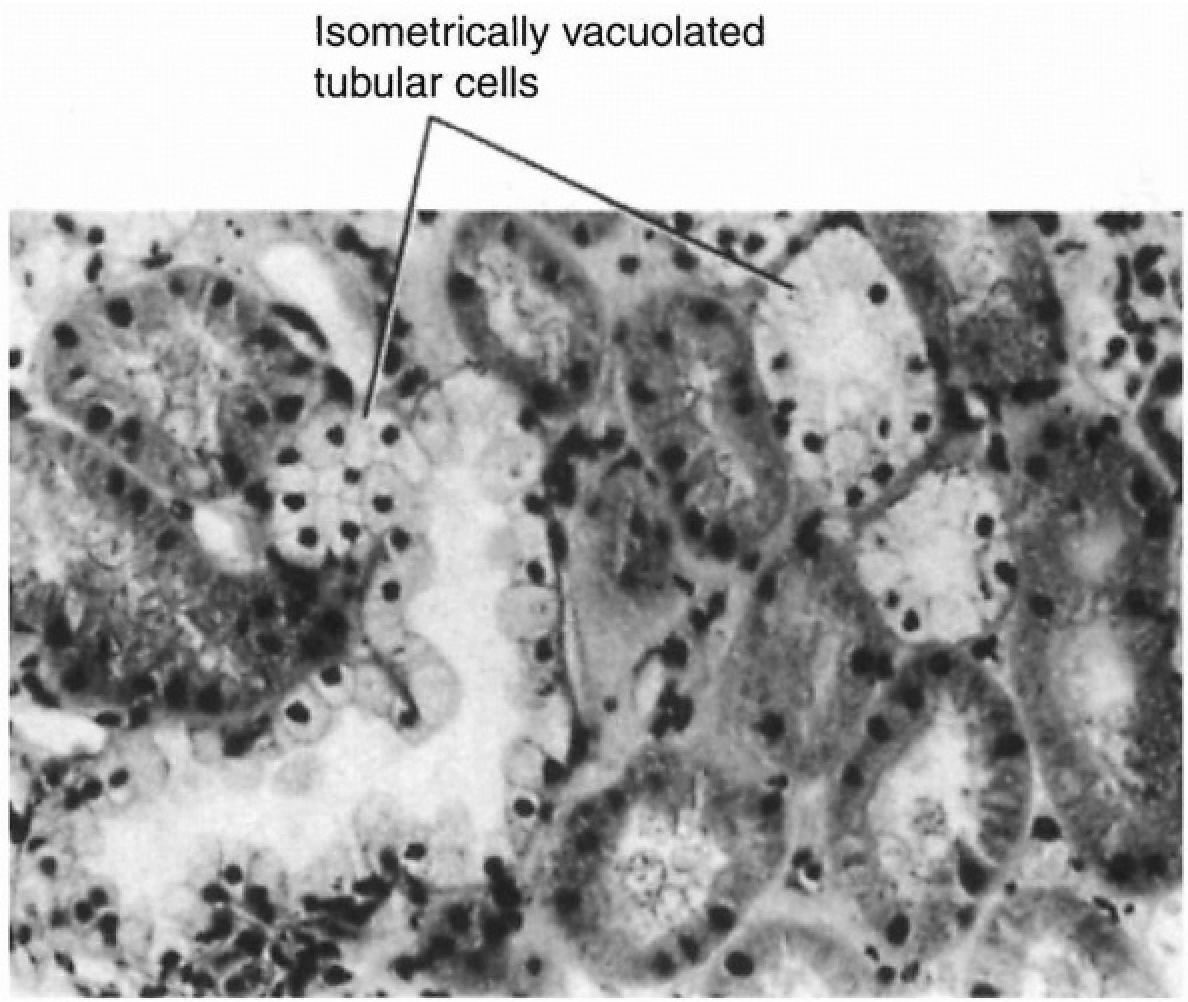


FIGURE 14.8 Cyclosporine toxicity with tubular cell isometric vacuoles. The cells of the lighter-staining tubules contain numerous closely packed uniform vacuoles. Note the lack of interstitial edema or inflammation. (Hematoxylin and eosin stain, ×200.)

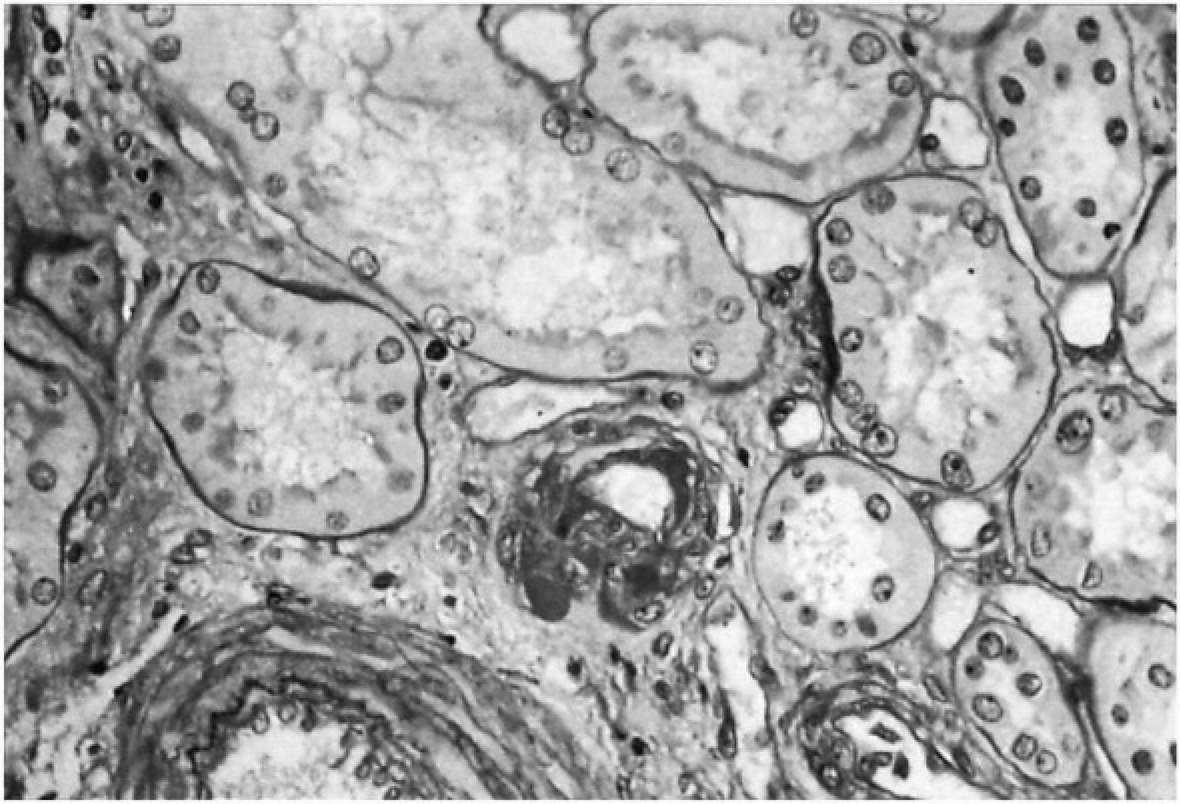


FIGURE 14.9 Cyclosporine-associated arteriolopathy. The arteriole has plasma protein insudates (“hyalinization”) along the outer aspect of the hypertrophied muscularis. There is no significant edema or inflammation in the interstitium. (Periodic acid-Schiff stain, ×285.)

Chronic Toxicity

The changes of chronic calcineurin inhibitor toxicity are similar to chronic renal ischemia. In their purest form, they consist of focal fibrosis, or “striped” *interstitial fibrosis,* and tubular atrophy without inflammation. The interstitium may show a generalized increase of collagen types III and IV with lesser increases in type I. Glomerular ischemic collapse or complete sclerosis is also present. These features appear not to be a consequence of intrarenal arterial narrowing because the arteries are largely unremarkable; therefore, the combination of normal arteries with a vascular pattern of parenchymal fibrosis is highly suggestive of chronic calcineurin inhibitor nephrotoxicity. Juxtaglomerular apparatus hyperplasia may be pronounced.

Differential Diagnosis

As discussed previously, differentiation between nonspecific interstitial fibrosis and tubular atrophy, nephrosclerosis, and chronic calcineurin inhibitor nephrotoxicity may

be difficult. Perhaps the most salient feature permitting this distinction is the status of the interlobular and arcuate arteries, which are often fortuitously included in the biopsy. Normal arteries usually indicate chronic calcineurin inhibitor nephrotoxicity. Intimal and medial fibrosis of arteries, often with lymphocytic infiltrates, are diagnostic of chronic rejection. If the arteries disclose the usual features of hypertension, nephrosclerosis is likely. These three lesions may coexist and cloud the picture. In addition, characteristic vascular findings may only be present in large arcuate and interlobar arteries and thus may not be included in a core biopsy specimen, further causing diagnostic difficulty.

OTHER PATHOLOGIC TRANSPLANT LESIONS

Acute Tubular Necrosis

Acute tubular necrosis in transplants is similar histologically to the lesion found in native kidneys, although there may be more overt necrosis of epithelial cells and sloughing of nonpyknotic epithelium into tubular lumens (Fig. 14.10). It is most often encountered in a biopsy performed within the first month or so after transplantation because of delayed graft function (see Chapter 9). In addition to the usual changes of tubular necrosis, focal interstitial lymphocytic infiltrates may be present without tubular inflammation.

Infections

Although the transplanted kidney may be the site of various infections, it may be difficult to diagnose them on the basis of tissue examination. This is not the case for usual forms of acute bacterial interstitial nephritis (acute pyelonephritis), in which the predominant cells infiltrating the interstitium and tubules are polymorphonuclear leukocytes. Some uncommon nonsuppurative bacterial infections, however, are characterized by mononuclear leukocytic tubular and interstitial infiltrates. Viral infections typically produce a mononuclear tubulointerstitial nephritis, which may be morphologically similar to cell-mediated acute rejection, but may have a more prominent plasma cell inflammatory component. Specific agents, such as cytomegalovirus (CMV), may be difficult to diagnose because intranuclear or cytoplasmic inclusions are rare.

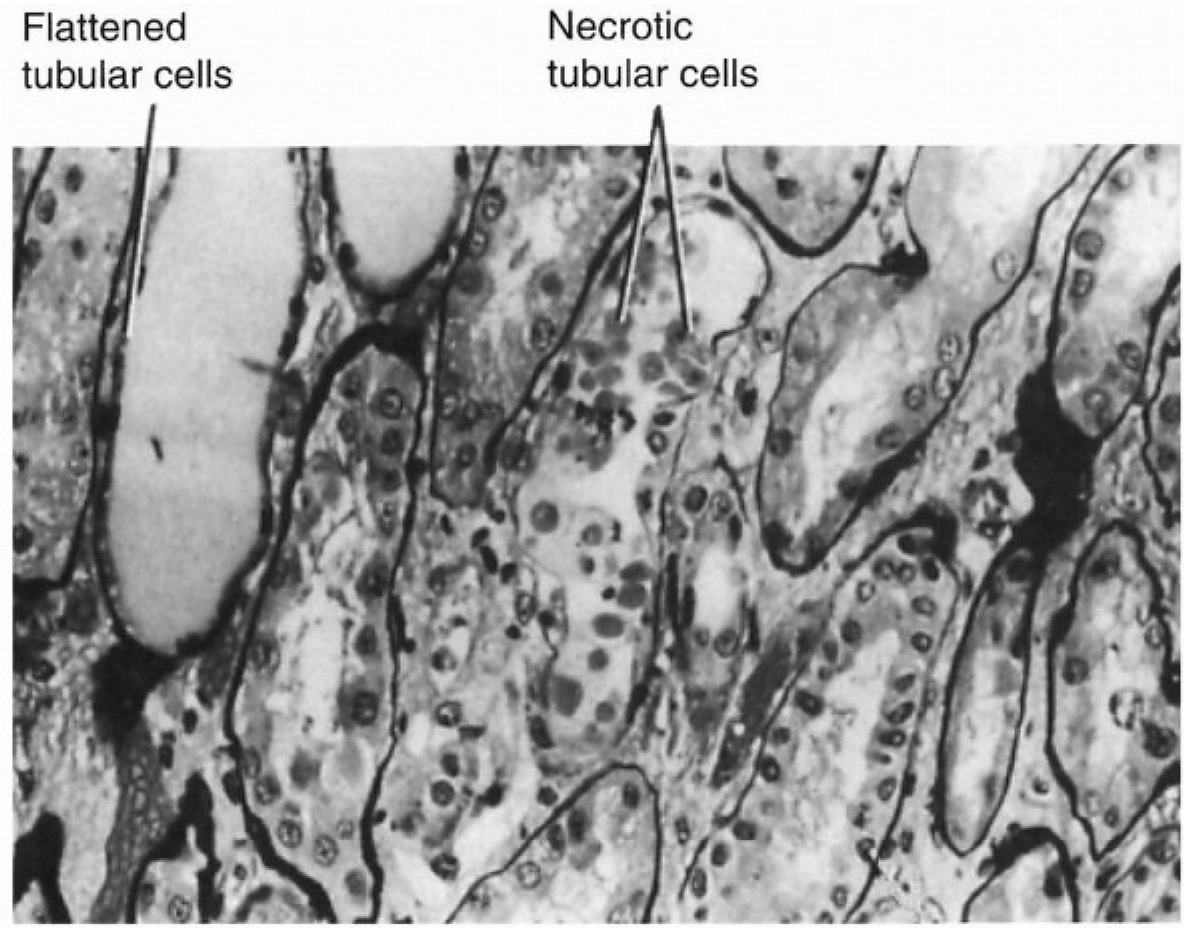


FIGURE 14.10 Acute tubular necrosis. The tubule in the center is incompletely lined by epithelial cells; sloughed cells and cellular debris are in the lumen. There is mild interstitial edema with few accompanying lymphocytes. (Periodic acid-methenamine silver stain, ×250.)

Human Polyomavirus Infection

Human polyomavirus BK infection has become a more frequently recognized infectious agent in immunosuppressed patients (see Chapter 10). Infection presents clinically as an elevated creatinine level with biopsy findings suggestive of severe acute rejection. If the diagnosis is unrecognized and immunosuppression is intensified, renal function will typically deteriorate further. Polyomavirus infection may also be associated with ureteric stenosis (see Chapter 8). In biopsy specimens with severe tubulointerstitial nephritis, infection is suggested by a patchy or focal inflammatory infiltrate with many plasma cells, and the finding of large basophilic intranuclear inclusions, occasionally with central clearing in enlarged tubular epithelial cells (Fig 14.11). The inflammatory infiltrate may be mild and associated only with tubules containing infected cells. Special staining with polyomavirus monoclonal antibody confirms the diagnosis.

The varying histology found in this viral infection was assessed by Drachenberg, who developed a classification of histologic patterns of injury in polyomavirus nephropathy

that correlates with clinical outcome. Recently, polyomavirus infection has been associated with tubular basement membrane immune complex deposition.

De Novo Glomerulopathies

De novo membranous glomerulonephritis is found in up to 10% of kidneys in place for more than 1 year, and the capillary wall deposits are not infrequently combined with features of chronic injury. Membranous glomerulonephritis is

often clinically silent or mild and is usually detected as an incidental finding. Focal and segmental glomerulosclerosis, including the usual and collapsing types, may occur as an independent lesion, although it often accompanies transplant glomerulopathy and may be associated with heavy proteinuria. Other forms of *de novo* glomerulonephritis are uncommon. The most reliable manner in which to diagnose these lesions is with immunofluorescence and electron microscopy, as for native kidney glomerular disease, because the deposits and basement membrane changes often are not readily visible by light microscopy or are overshadowed by transplant glomerulopathy.

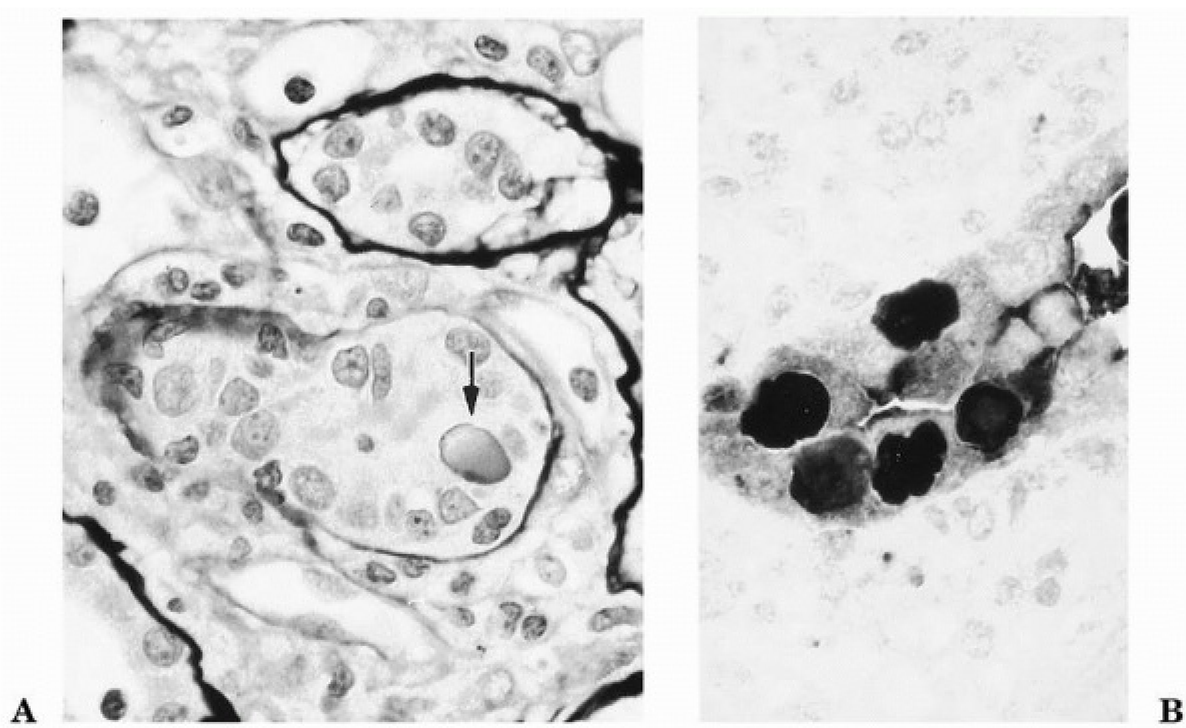


FIGURE 14.11 Polyoma virus infection. A: Tubular cells are enlarged with nuclear viral inclusions *(arrow)* and show necrosis. There is an adjacent lymphocytic inflammatory infiltrate (Jones methenamine silver, ×225). B: Immunoperoxidase stain for SV40 (polyomavirus) showing positive staining in infected tubular epithelial cells (×250).

Recurrent Lesions

Glomerular Lesions. Although a variety of glomerulonephritides may recur during the post-transplantation course, the recurrences are often of immunopathologic rather than clinical significance and do not necessarily affect graft survival or function (see Chapter 10). Overall, 6% to 20% of renal allograft recipients develop *de novo* or recurrent glomerular lesions. These lesions include IgA nephropathy, membranoproliferative glomerulonephritis type I and type II (dense deposit disease), and, occasionally, membranous glomerulonephritis. Focal and segmental glomerulosclerosis has a 20% to 30% recurrence rate, may recur early after engraftment, and is the recurrent lesion most likely responsible for graft loss. Antiglomerular basement membrane disease rarely recurs but can arise in a normal kidney transplanted into a patient with Alport syndrome (see Chapter 6). Other glomerulonephritides, such as lupus glomerulonephritis and vasculitis with crescentic glomerulonephritis, recur after transplantation, but not frequently.

Other Lesions. Amyloidosis, multiple myeloma, light-chain deposition disease, hemolytic uremic syndrome, and oxalosis can recur, often with significant graft dysfunction. The structural changes of diabetic nephropathy, including patients with diabetes as the primary renal disease and those with post-transplantation diabetes, may occur in the renal allograft but are infrequently responsible for

---

graft loss (see Chapter 15). Nodular and diffuse glomerulosclerosis and arteriolar hyalinization are the usual morphologic manifestations of the recurrent lesion.

CLASSIFICATION SCHEMA

In an attempt to develop an organized and consistent approach to the classification and grading of the various structural lesions in the transplanted kidney, a series of workshop-type conferences was held in Banff, Canada. The resulting schema, which came to be known as the *Banff classification,* was then combined with a separately developed classification resulting from a National Institutes of Health-sponsored study (Cooperative Clinical Trials in Transplantation). This classification scheme has undergone further modification and is most complete for acute rejection, although chronic lesions also are addressed.

There are two parts to the schema: (1) the diagnostic classifications, and (2) the grading of each pathologic component in the tissue sample. The grading is somewhat cumbersome and involves assigning a degree of severity to changes affecting the tubules, interstitium, vessels, and glomeruli. The diagnostic categories include antibody-mediated rejection; a borderline lesion; cell-mediated rejection; chronic tubulointerstitial changes without specific etiology; and other changes not due to acute or chronic rejection. Table 14.2 summarizes the important aspects of the current Banff classification, including the Banff 2005 update.

According to the Banff classification, mild (<25%) interstitial lymphocytic infiltration with any degree of tubular inflammation or mild tubulitis (one to four lymphocytes per tubular cross section) in the absence of arterial intimal inflammation is considered a *borderline lesion,* suspicious for acute rejection. There remains some controversy regarding the clinical significance of borderline lesions; some studies associate these lesions with treatment-responsive clinical acute rejection. The grade III rejection criteria do, however, appear to correlate with more severe clinical rejections, which may be unresponsive to treatment with high-dose steroids alone (see Chapter 4). The Banff classification with the 2005 modifications incorporates our increasing understanding of the mechanisms of graft injury, and this grading scheme undoubtedly will undergo further revisions as there is greater understanding of morphologic features in renal allografts biopsies, such as the role of B cells and monocyte-macrophages. Additional work also is required to clarify the clinical usefulness of the revised Banff classification, and as the classification scheme is modified further, validation in clinical studies will need to be done. Finally, a limitation of any grading scheme is of concern regarding the consistency of grading between observers.

NEW TECHNIQUES IN EVALUATING TRANSPLANT DYSFUNCTION

The evaluation of acute and chronic renal allograft dysfunction is an area ripe for the application of new technologies, including gene profiling with microarrays, metabolomics, and proteomics. In one such study, microarrays have been used in experimental models to create pathogenesis-based transcript sets (PBTs) that reflect biologic events in allograft rejection. These PBTs then were correlated with histopathology and clinical diagnoses in human kidney transplant biopsies. PBTs correlated strongly with one another and with histopathologic lesions; the highest were found in biopsies with clinically apparent rejection episodes. Thus, information gleaned from microarrays may be used to quantitate the inflammatory disturbances in organ transplants, investigate the mechanisms of these changes, and monitor response to treatment. In addition, PBTs suggested that some current Banff histopathology criteria are unreliable, particularly at the cutoff between borderline and rejection, and may allow further refinement of morphologic classification. Technology is being used to identify markers such as FOXP3 for diagnosis of rejection and response to therapy. A defined collection of genes in renal biopsy specimens has been found to be predictive of chronic rejection before clinical or histologic features of chronic damage. In addition, noninvasive methods for identifying rejection also are being explored and have demonstrated proteomics of urine specimens as a potential tool in this area. The goal is to correlate genomic, proteomic, and post-translational protein modification data with clinical information and biopsy morphology to afford early diagnosis and targeted treatment for rejection and other causes of early and late transplant dysfunction.

KIDNEY DONOR HISTOPATHOLOGY

The gap between the supply and demand for cadaveric kidneys has led to the increasing use of organs from "marginal" and "extended criteria" donors (see Chapters 4 and 7). Histopathology of these kidneys often is requested as a guide to the wisdom of transplanting a particular organ. The most common clinical situations in which donor pathology is requested are for older donors, donors with a history of hypertension or vascular disease, or donors with preharvesting evidence of renal dysfunction. Baseline histology may be required in the clinical trials evaluating new immunosuppressive drugs.

The time constraints imposed by the need for rapid decision making prevent routine histopathologic processing of biopsy material. Use of frozen tissue may impair diagnostic precision, and rapid-processing techniques are preferred. A superficial wedge biopsy specimen may be provided; however, the subcapsular parenchyma often has chronic changes and is not representative of the whole organ. Additionally, arteries may be absent from superficial biopsy specimens, precluding adequate evaluation for nephrosclerosis. Therefore, such specimens should be interpreted with caution. The number and percentage of sclerosed glomeruli should be determined and an assessment made of the degree of tubulointerstitial and vascular disease. Transplant teams tend to give more prognostic credence to numeric values that may reflect the degree of nephrosclerosis, and kidneys with more than 20% sclerosed glomeruli often are discarded. However, interstitial and vascular changes, which are more difficult to quantitate in this setting, may have more prognostic importance.

Selected Readings

Anglicheau D, Sharma V, Ding R, et al. MicroRNA expression profiles predictive of human renal allograft status. Proc Natl Acad Sci 2009;106:5330-5335.

Audard V, Matignon M, Dahan K, et al. Renal transplantation from extended criteria cadaveric donors: problems and perspectives overview. Transpl Int 2008;21:11-17.

Bhalla V, Nast C, Stollenwerk N, et al. Recurrent and *de novo* diabetic nephropathy in renal allografts. Transplantation 2003:75:66-69.

Bohmig GA, Exner M, Habicht A, et al. Capillary C4d deposition in kidney allografts: a specific marker of alloantibody-dependent graft injury. J Am Soc Nephrol 2002;13:1091-1099.

Choy BY, Chan TM, Lai KN. Recurrent glomerulonephritis after kidney transplantation. Am J Transplant 2006;6:2535-2542.

Clark W, Silverman BC, Zhang Z, et al. Characterization of renal allograft rejection by urinary proteomic analysis. Ann Surg 2003;237:660-664.

Colvin RB. Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. J Am Soc Nephrol 2007;18:1046-1056.

Colvin RB. Chronic allograft nephropathy. N Engl J Med 2003;349:2288-2290.

Colvin RB. Pathology of chronic humoral rejection. Contrib Nephrol 2009;162:75-86.

Hever A, Nast CC. Polyoma virus nephropathy with simian virus 40 antigen-containing tubular basement membrane immune complex deposition. Hum Pathol 2008;39:73-79.

Mueller TF, Einecke G, Reeve J, et al. Microarray analysis of rejection in human kidney transplants using pathogenesis-based transcript sets. Am J Transplant 2007;7:2712-2722.

Naesens M, Kuypers, D, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol 2009;4:481-508.

Nankivell BJ, Chapman JR. Chronic allograft nephropathy: current concepts and future directions. Transplantation 2006;81:643-654.

Nickeleit M, Andreoni K. Infalmmatory cells in renal allografts. Front Biosci 2008;13:6202-6213.

Racusen LC, Halloran PF, Solez K. Banff 2003 meeting report: new diagnostic insights and standards. Am J Transplant. 2004;4:1562-1566.

Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int 1999;55:713-723.

Randhawa P, Brennan DC. BK virus infection in transplant recipients: an overview and update. Am J Transplant 2006;6:2000-2005.

Solez K, Colvin RB, Racusen LC, et al. Banff '05 meeting report: differential diagnosis of chronic allograft injury and elimination of chronic allografts nephropathy. Am J

Transplant 2007;7:518-526.

Wishart DS. Metabolomics in monitoring kidney transplants. Curr Opin Nephrol Hypertens 2006;15:637-642.

Yilmaz S, Tomlanovich S, Mathew T. Protocol core needle biopsy and histologic chronic allograft damage index (CADI) as surrogate end point for long-term graft survival in multicenter studies. J Am Soc Nephrol 2003;14:773-779.

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

15

Kidney and Pancreas Transplantation in the Diabetic Patient

Gerald S. Lipshutz

Diabetes mellitus is a major health problem worldwide, affecting as many as 135 million people. In the United States, it affects about 6% of the population (18 million individuals), with at least half being unaware that they have the disease. It accounts for more than 160,000 deaths each year in the United States, and in 2002, the annual direct and indirect costs of type 1 and 2 diabetes exceeded $130 billion. The prevalence of type 1 diabetes in the United States is estimated to be 1,000,000 people, with 30,000 new cases diagnosed each year, and this has not substantially changed in the recent past.

At the turn of the 19th century, a patient diagnosed with type 1 diabetes had an average life expectancy of 2 years. However, with the isolation and development of insulin as a treatment for diabetes, the disease has been changed from one that is rapidly fatal to a chronic disease with the potential for multiple secondary complications within 10 to 20 years after disease diagnosis. These include blindness, cardiovascular disease, dyslipidemia, cerebrovascular disease, amputation, and life-span reduction.

Diabetes mellitus is the leading cause of end-stage renal disease (ESRD), accounting for about one third of new dialysis-dependent patients each year. About 40% of the ESRD population has diabetes, and most have type 2 diabetes. The incidence of ESRD as a consequence of type 2 diabetes is increasing in all countries with a Western diet and lifestyle. Because of the growth in diabetes in the population, the number of diabetic patients with new ESRD has surpassed the number of patients with ESRD from all other primary diagnoses and most commonly leads to kidney transplantation in adult whites, Asians, and Native Americans. In addition to ESRD, major complications in these patients include retinopathy, which is the second leading cause of blindness in all persons, and peripheral vascular disease. Ten percent of diabetic patients require a major amputation in their lifetime. Life expectancy is about one third lower in diabetic patients compared with nondiabetic patients, and cardiovascular disease is the leading cause of death.

For many patients with type 1 diabetes mellitus, the treatment of choice is a whole vascularized pancreas transplantation. As of the end of 2004, more than 23,000 pancreas transplantations had been performed worldwide, and through 2006, more than 20,000 pancreas transplantations were performed in the United States. Since 2000, the 1-year patient survival rate for simultaneous pancreas and kidney (SPK) transplantation, pancreas after kidney (PAK) transplantation, and pancreas transplantation alone (PTA) were 95% to 97%, and the 1-year pancreas graft survival rates were 85%, 78%, and 77%, respectively.

The potential benefits of a pancreas and kidney transplantation in a patient with type 1 diabetes and renal failure are improved quality of life, prevention of recurrent diabetic nephropathy, freedom from exogenous insulin with euglycemia and normalization of glycosylated hemoglobin, lack of frequent whole blood glucose monitoring, lack of dietary restrictions, and stabilization or improvement in secondary complications. The benefits of an SPK are the basis of its acceptance as an appropriate therapy for patients with type 1 diabetes mellitus and renal failure. The tradeoff for the patient is the operative risk

and the need for lifelong chronic immunosuppression. Pancreas transplantation is the ultimate intensification of insulin therapy because it normalizes glucose levels far better than any other strategy available for the treatment of type 1 diabetes mellitus. In this chapter, the issues concerning pancreas transplantation in type 1 diabetic patients are presented. The indications for, technical differences between, and management of the different methods of pancreas transplantation are discussed. The special concerns regarding kidney transplantation in both type 1 and type 2 diabetic patients are discussed in Chapters 7 and 10. Figure 15.1 illustrates the whole-organ transplantation options available for type 1 diabetic patients with advanced renal disease and ESRD.

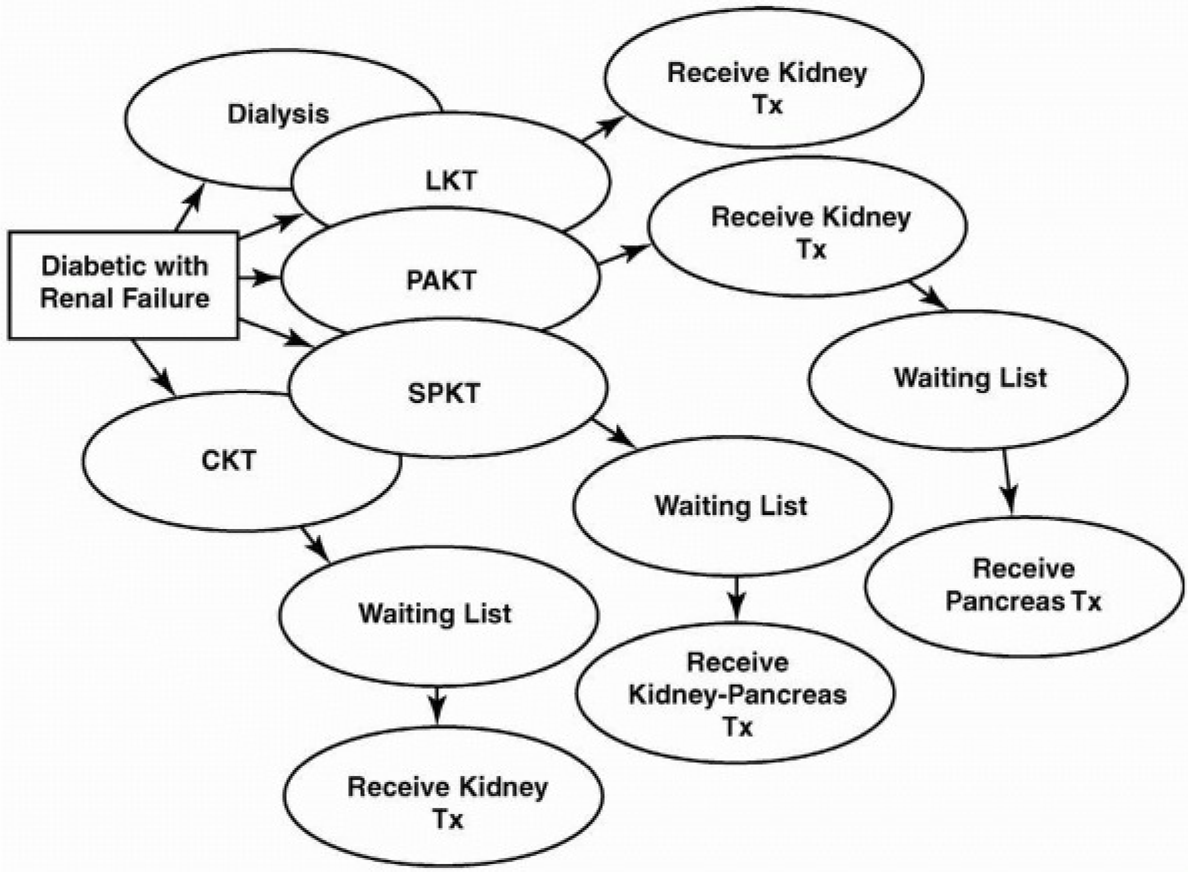


FIGURE 15.1 Options for diabetics with renal failure. A diabetic patient with renal failure can choose one of five treatment strategies: dialysis, living kidney transplantation (LKT), pancreas after living kidney transplantation (PAKT), simultaneous pancreas and kidney transplantation (SPKT), or deceased donor kidney transplantation (CKT). (From Knoll GA, Nichol G. Dialysis, kidney transplantation, or pancreas transplantation for patients with diabetes mellitus and renal failure: a decision analysis of treatment options. J Am Soc Nephrol 2003;14:500-515, with permission.)

HISTORY OF PANCREAS TRANSPLANTATION

The first human pancreas transplantation was performed in 1966 by William Kelly and Richard Lillehei at the University of Minnesota. The major surgical challenge that needed to be overcome was a method of pancreatic exocrine drainage. A duct-ligated segmental pancreatic allograft and a deceased donor kidney were transplanted into a 28-year-old woman with type 1 diabetes mellitus and ESRD. Post-transplantation immunosuppression was azathioprine and prednisone. A pancreatic fistula complicated the patient's postoperative course, and both the kidney and pancreas were removed about 2 months later. Subsequently, the patient died from a pulmonary embolus. The second patient, a 32-year-old recipient, was transplanted 2 weeks after the first recipient. The

patient suffered from rejection and was treated with steroid boluses and graft irradiation. The patient died from sepsis 41/2 months after transplantation.

Although these initial results were individually poor, they were at the same time encouraging in that these early transplantations did demonstrate that glucose control without exogenous insulin was possible. The procedure established that endogenous secretion of insulin with normal feedback mechanisms could occur with a whole-organ vascularized pancreas transplantation.

SURGICAL OPTIONS FOR DIABETIC PATIENTS

There are three major procedures for type 1 diabetic patients who are considering whole-organ pancreas transplantation. First is the SPK transplantation for diabetic patients with advanced renal disease or ESRD. A major advantage of SPK transplantation is that there is only one surgical intervention and one source of foreign human leukocyte antigen (HLA) to which the patient is exposed. The largest numbers of pancreas transplantations are performed as SPK transplantations (Fig. 15.2). Chronic immunosuppressive therapy is similar to that which these patients would receive with a kidney transplant alone. As in PAK transplantation, however, many patients have already suffered substantial secondary diabetic complications, and the extent to which these complications will reverse or stabilize is uncertain. Regardless, SPK transplantation is established as a therapeutic and effective procedure, and not only is it lifesaving for the type 1 diabetic patient, but also numerous studies have demonstrated that it is life enhancing, with a significant overall improvement in quality of life indices over kidney transplantation alone. Among pancreas recipients, those with an SPK transplantation had the best pancreas graft survival rates: 86% at 1 year and 54% at 10 years (Figs. 15.3 and 15.4).

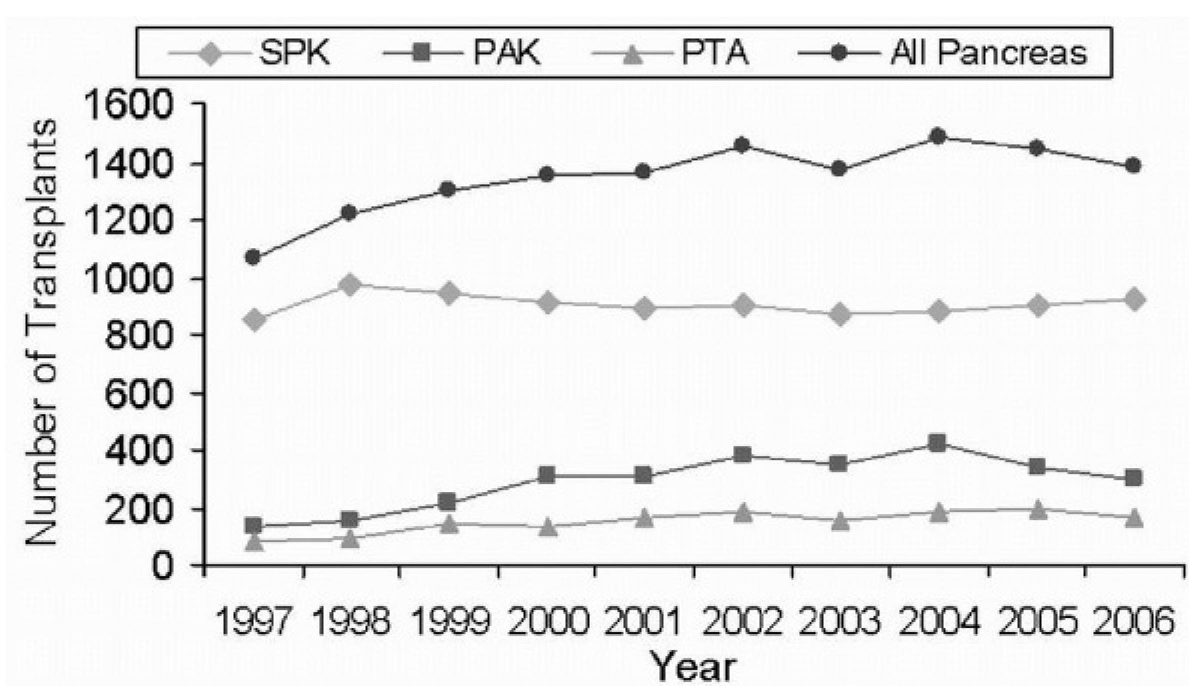


FIGURE 15.2 The overall number of pancreas transplants increased from 1,062 in 1997 to 1,483 in 2004. The largest number of pancreas transplants are simultaneous pancreas and kidney transplantations, accounting for 67% of all pancreas transplants in 2006. (From 2007 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Transplant Data 1997 2006. Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD, with permission.)

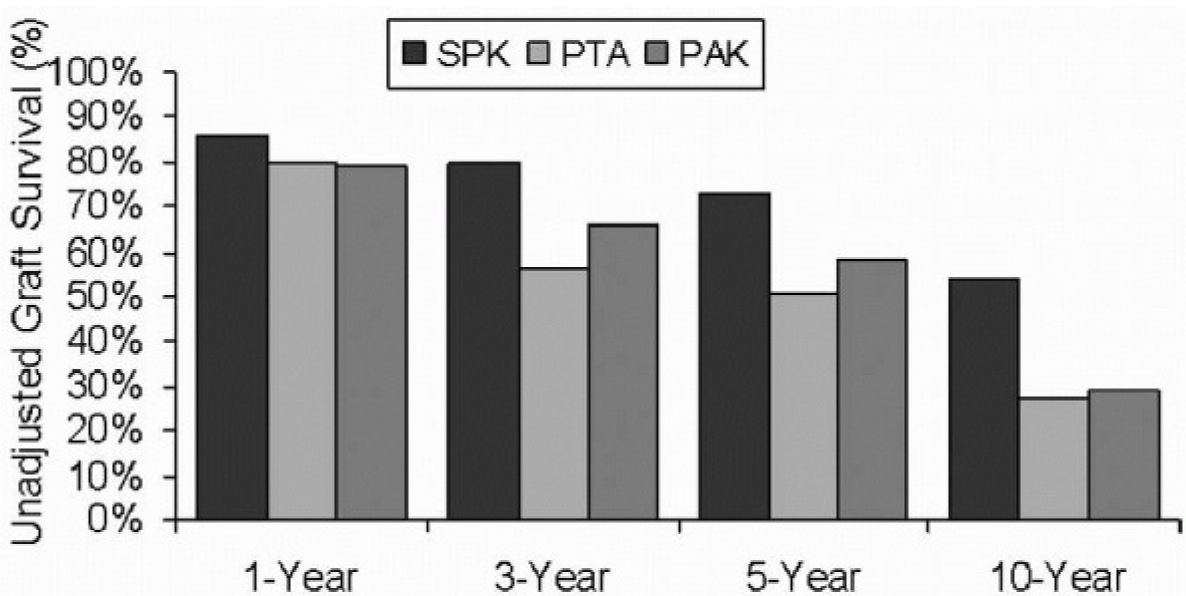


FIGURE 15.3 Among pancreas transplant recipients, those with simultaneous pancreas and kidney transplants experienced the highest pancreas graft survival rates: 86% at 1 year and 54% at 10 years. Graft survival rates for pancreas after living kidney and pancreas transplant alone recipients were similar to one another at 1 year (79% and 80%, respectively) and 10 years (29% and 27%, respectively). (From 2007 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Transplant Data 1997 2006. Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD, with permission.)

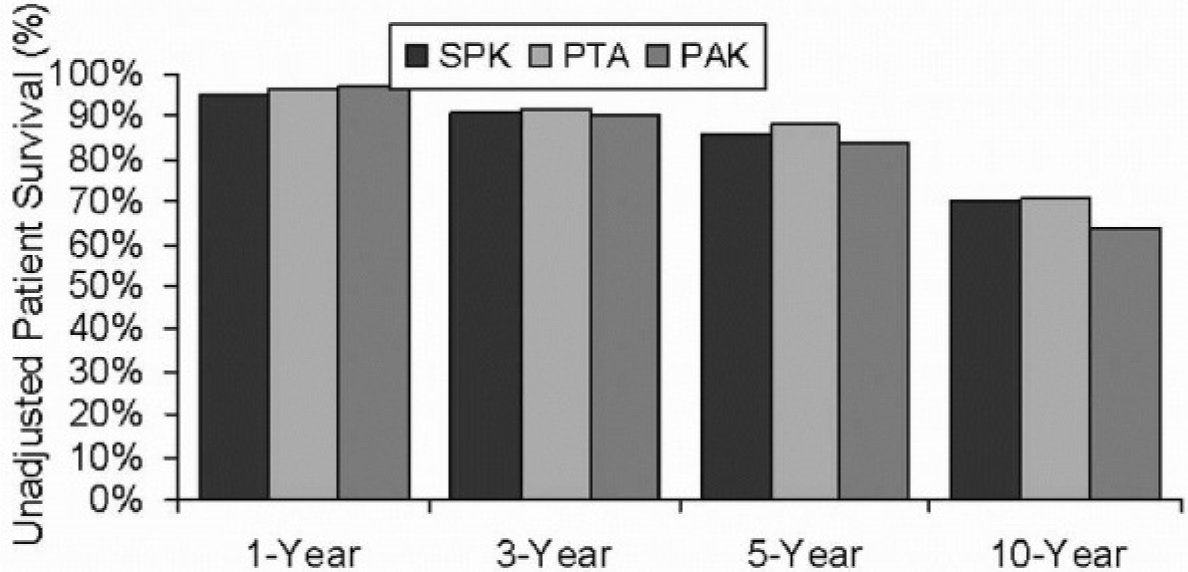


FIGURE 15.4 Patient survival rates were similar for pancreas after kidney (PAK), simultaneous pancreas and kidney (SPK), and pancreas transplant alone (PTA) 1, 3, and 5 years after transplantation. The 10-year patient survival rate was lowest for PAK at 64% and similar for SPK and PTA recipients, with rates of 70% and 71%, respectively. (From 2007 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Transplant Data 1997 2006. Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD, with permission.)

Second is PAK transplantation for the diabetic patient who is already the recipient of a functioning kidney allograft. Immunosuppressive therapy is not the major concern because these patients are already receiving chronic immunosuppression. The main risk to the patient is the alteration in immunosuppression necessary after pancreas transplantation. This alteration can negatively affect postoperative renal function because immunosuppressant levels are often increased in these recipients compared with renal transplant alone recipients. In addition, there is the inherent risk for an intra-abdominal surgical procedure. PAK transplantation may be a particularly important option for patients with a living donor, in which case the kidney is placed in the left iliac fossa in anticipation of pancreas transplantation in the future. The graft survival rate for PAK recipients at 1 year is 79%, with a 10-year survival rate of 29% (Fig 15.3).

PAK recipients have already suffered significant secondary diabetic complications. Other than making these recipients insulin independent, it is uncertain whether a well-functioning pancreatic allograft will have any additional benefit in the long-term. Overall, the results of PAK transplantation are worse than those of SPK transplantation, likely related to difficulties in diagnosing pancreatic allograft rejection because the

kidney (owing to differing HLA) is now longer available as surrogate to assess for rejection by biopsy. It is the second most common pancreas transplant operation. In 1999, Medicare-approved reimbursement for pancreas transplantation for patients with ESRD (i.e., those receiving an SPK and PAK but not PTA), making the procedure available for a much larger population of patients.

The third method, and by far the least common, is pancreas transplantation alone (or PTA) in the preuremic recipient. This is a therapeutic option for diabetic patients with minimal to no renal dysfunction who have brittle diabetic control despite the administration of insulin. Many also have hypoglycemic unawareness. The main risks to these patients are the long-term effects of chronic immunosuppression, not only on native renal function but also in the development of atherosclerosis and increased risk for malignancy, and the surgical procedure itself. The number of patients receiving these transplants has increased, likely due in part to improvements in immunosuppression. In 2004, less than 250 patients underwent PTA in the United States. One-year graft survival rates for PTA recipients is 80%, with a 10-year rate of 27% (Fig 15.3). The American Diabetes Association (ADA) criteria for PTA are as follows:

- Consistent failure of intensive insulin-based therapy to establish reasonable glycemic control and to prevent secondary complications
- Incapacitating clinical and emotional problems with exogenous insulin therapy

There is controversy regarding the survival benefit with PTA because of its associated morbidity and mortality, the need for immunosuppression, and questions about whether secondary complications are prevented. Most centers only consider the procedure in diabetic patients with severe hypoglycemic unawareness or significant secondary complications of diabetes without renal dysfunction. The option of islet transplantation on these patients is discussed later.

EVALUATION OF THE PANCREAS TRANSPLANTATION CANDIDATE

Recipient selection and pretransplantation evaluation are essential to avoid significant transplant-related complications. Waitlist candidates should be seen and examined routinely while awaiting organ transplantation. Specific studies should be repeated if the patient remains on the waitlist for a prolonged period of time.

Coronary Artery Disease

Serious vascular complications limit the success of transplantation in diabetic patients. These patients often have multiple cardiovascular risk factors in addition to the long history of diabetes mellitus. These often include tobacco use,

hypertension, hyperlipidemia, family history, and renal failure. Nearly half of diabetic transplant recipients die within 3 years after transplantation from a vascular complication, and in pancreas transplant recipients, cardiovascular disease is the single greatest cause of death. Type 1 diabetes patients are at particularly high risk for premature coronary atherosclerotic disease, with as many as 35% dying of coronary artery disease by age 55 years. Coronary artery disease prevalence increases significantly with age and has been found in most patients older than 45 years. The risk for death in these patients is increased 8- to 15-fold in patients with nephropathy.

Most of these patients do not suffer typical anginal symptoms, and thus the possibility of unknown coronary artery disease should be considered in every diabetic patient being considered for organ transplantation. All patients should undergo appropriate evaluation preoperatively according to general recommendations documented in Chapter 7. The precise protocol used is controversial and center specific. The controversy is likely related to the poor predictive value of noninvasive imaging in diabetic transplant candidates. Nuclear perfusion imaging is best performed as a screening study. In general, young patients who have had diabetes mellitus for less than 25 years, have not smoked tobacco, and lack other cardiovascular risk factors may be evaluated by stress imaging alone. A treadmill nuclear stress test used with thallium or sestamibi scintigraphy or echocardiography is an appropriate initial study. Many diabetic patients with ESRD, however, have poor exercise tolerance and are unable to obtain a rate of 85% of their predicated maximal heart rate. These patients should undergo an adenosine nuclear stress test or a dobutamine stress echocardiogram designed to replicate the effect of exercise stressing on cardiac function.

Most other candidates should be evaluated by coronary angiography, and significant coronary artery disease should be appropriately treated before undergoing transplantation. In addition, patients are generally recommended to undergo routine annual reassessment with noninvasive stress imaging until transplanted, although the benefit of this commonly used strategy had not been prospectively documented. The fact that these patients have had longstanding diabetes should not be forgotten after a successful pancreas transplantation. Risk factor modification should continue throughout the pretransplantation and post-transplantation periods.

Pancreas transplant candidates with multiple risk factors or a positive nuclear stress test should undergo cardiac angiography and evaluation by a cardiologist before candidacy determination. Patients with coronary lesions amenable to bypass grafting or angioplasty and stent placement should be treated before transplantation. If patients require a postprocedure course of clopidogrel bisulfate, it is preferable that this be completed before undergoing transplantation. However, patients with significant coronary artery disease that is not amenable to interventional cardiology or surgical therapy should not be considered candidates for pancreas transplantation.

Aggressive risk factor modification including statins for elevated lowdensity lipoprotein cholesterol and total cholesterol should be instituted. When possible, patients should be

started on low-dose β blockade if they do not have hypoglycemic unawareness of other contraindications. β_1-Selective blockers are preferable to avoid undesirable side effects. Antihypertensive drugs that do not aggravate insulin sensitivity or lipid metabolism should be selected for treatment of arterial hypertension. β_1 Blockers without intrinsic sympathomimetic action are preferable for patients with both diabetes and hypertension and with associated ischemic heart disease, whereas β_1 blockers with intrinsic sympathomimetic action, exerting a vasodilative action, are useful for diabetic hypertensive patients without ischemic heart disease because they do not aggravate

---

insulin sensitivity and lipid metabolism. In addition, daily aspirin and omega-3 and omega-6 fatty acids should be recommended to promote vascular health.

Cerebrovascular and Peripheral Vascular Disease

The increased susceptibility of diabetic transplant recipients for cerebrovascular and peripheral vascular disease mandates particular attention to these issues in the pretransplantation evaluation. About 4% of kidney alone and SPK recipients experience a stroke or transient ischemic attack in the 4-year postoperative evaluation period; nearly one third of these are fatal. Any history of cerebrovascular events or intermittent claudication or findings of carotid or femoral bruits or poor peripheral pulses should be further assessed during patient evaluation. Further consultation with a vascular surgeon may be necessary.

Infections

Patients should be free of significant infections, such as peritonitis, osteomyelitis, or unhealed foot or lower extremity ulcerations at the time of transplantation. Close examination of the patient's feet and lower extremities should be performed at each visit and on admission for organ transplantation. If a patient is admitted to undergo transplantation and a lower extremity ulcer is found, that patient should be discharged and should notify the transplantation center when it is completely healed. Significant dental decay and periodontal disease should also be treated before transplantation. Patients should be informed that if they develop infectious complications while awaiting transplantation, their candidacy will be placed “on hold” until all infectious issues have been resolved.

Predialysis Transplantation

The advantages of predialysis transplantation for kidney transplant candidates are discussed in Chapter 7; they also apply to candidates for SPK. Early transplantation can obviate the need for both temporary and permanent dialysis access and disfigurement of the extremities associated with these procedures, can prevent episodes of congestive heart failure and fluid overload, and can correct hypertension, which may

contribute to more rapid vision loss in this group of patients. Some data suggest that early transplantation may slow retinopathy and correct neuropathy. The development of diabetic complications on dialysis may impair the rehabilitation potential after transplantation.

Predialysis diabetic transplant candidates who require coronary angiography risk worsening of renal function and potential dialysis initiation induced by exposure to iodinated contrast agents. This risk of contrast-induced nephropathy has to be carefully weighed against the risks associated with undiagnosed coronary artery disease. Working closely with a cardiologist can be helpful in that the dose of intravenous contrast administered during coronary angiography can be minimized to reduce the risk for precipitating renal failure.

Insulin Requirements

By the time many diabetic patients develop advanced nephropathy or the need for dialysis, their insulin requirements have often diminished. Patients receiving peritoneal dialysis may have higher insulin needs owing to the use of dextrose containing dialysates. Pancreas transplant candidates should have a C-peptide level drawn to confirm they are insulinopenic; however, their history will likely confirm their diagnosis. In type 1 patients a C-peptide value should be undetectable, or less than 0.5 ng/mL. Although several centers do perform pancreas transplantation in insulinopenic type 2 diabetic patients, this has not been widely adopted.

It may be more difficult to achieve adequate postoperative insulin levels in recipients who have a daily insulin requirement of greater than 60 units.

Obese type 1 diabetic patients may have also developed insulin resistance, and an estimate of the pretransplantation insulin requirement may be helpful in assessing the need for exogenous insulin after transplantation. Some glucose intolerance can be seen in the early postoperative period owing to large doses of corticosteroids, carbohydrate intolerance, infusion of medications prepared in 5% dextrose, improved appetite, and the use of calcineurin inhibitors that may lead to periods of elevated blood glucose and increased insulin requirements. Type 1 diabetic patients should expect to be free of exogenously administered insulin after a successful transplantation.

DONOR SELECTION

Appropriate pancreas donor selection is key to avoiding complications relating primarily to vascular thrombosis and duodenal enteric leaks. The organ donor for pancreas transplantation is typically in the age range of 10 to 45 years with a traumatic mechanism as the cause of brain death. Donors whose death is defined by cardiac criteria (see Chapter 4) are not suitable for whole-organ pancreas donation. The donor should have had no previous pancreatic surgery or history of pancreatic trauma, or a diagnosis of diabetes mellitus. A HgbAlc level before procurement may help assess for

glucose intolerance. Hyperglycemia is a common occurrence during the management of brain dead patients and does not represent a contraindication to pancreas donation.

An increased incidence of allograft thrombosis and graft loss has been described when the donors are aged greater than 45 years or have died from cerebrovascular accidents. Pancreata originating from older donors have had higher rates of intra-abdominal infections, anastomotic or duodenal leaks, relaparotomy, and decreased graft survival. As a result, caution should be urged in accepting and using pancreata from organ donors older than 45 years. Weight and body mass are also important considerations. Although no strict criteria exist regarding donor weight, some centers consider a donor lower weight limit of 45 kg. This is primarily because of concern of the size of the pancreatic arterial vasculature for construction of the iliac Y-graft and risk for arterial graft thrombosis. Some centers, however, routinely use pancreata from small or even pediatric donors with good outcomes. Donors with a body mass index higher than 30 are avoided by many centers because of an increased incidence of fatty infiltration and subsequent increased risk for ischemia-reperfusion injury, infection, pancreatitis, and allograft thrombosis.

PANCREAS TRANSPLANTATION: SURGICAL TECHNIQUE

The surgical procedure can be divided down into three stages: (1) organ procurement, (2) back table pancreas preparation, and (3) pancreas transplantation.

Organ Procurement

Successful and uncomplicated pancreas transplantation requires meticulous allograft procurement and attention to detail in preparing the pancreas on the back table. There is no substitute for a skilled surgeon examining the pancreas during procurement and making an assessment of the suitability of the organ.

After opening the lesser sac, the gastrocolic ligament is divided, and the pancreas is closely examined and palpated. The aorta and venal cava are exposed, followed by division of the right gastroepiploic and pyloric vessels. Some centers perform a bowel decontamination procedure. A nasogastric tube may be advanced into the second portion of the duodenum, and 200 mL of saline and povidone-iodine with amphotericin B is instilled. The short gastrics are ligated, the transverse colon is completely mobilized, and the stomach is then divided proximal to the pylorus. The fourth portion of the duodenum is

similarly divided, however, just before removal of the pancreas. With careful retraction of the spleen by a no-hands technique, the splenonephric and splenophrenic attachments are carefully divided. The liver is mobilized, and the aorta, vena cava, and inferior mesenteric vein are isolated. The gallbladder is emptied, and the bile duct is divided. The supraceliac aorta is isolated, and heparin is given intravenously. Cannulas are placed into the aorta and inferior mesenteric vein. In coordination with

the cardiothoracic team, the aorta is cross-clamped, and preservation solution is instilled along with surface cooling with ice slush. The thoracic organs are then procured, followed by removal of the liver after division of the gastroduodenal artery, portal vein, and splenic artery. The pancreas with spleen attached is then removed (Plate 15.1). The allograft is kept ice cold in sterile preservation solution until ready to be prepared on the back table.

Back Table Pancreas Preparation

The back table preparation of the pancreatic allograft requires careful surgical technique. It can be divided into four steps. First, the distal and proximal duodenum must be shortened to proper length. This is performed while probing the common bile duct at the ampulla to ensure that it is not compromised during duodenal shortening. The ends of the duodenum are generally stapled and then oversewn. The bile duct is ligated. A culture of the excised duodenum should be sent to the laboratory for Gram stain, fungal stain, and bacterial and fungal cultures. Second, arterial reconstruction is required. An arterial Y-graft is used with

---

the donor common iliac-external iliac-internal iliac artery bifurcation. The internal iliac artery is anastomosed to the splenic artery, and the external iliac artery is anastomosed to the superior mesenteric artery. The inferior mesenteric vein is ligated. The portal vein should be separated from the surrounding tissue. An extension graft is rarely required and should be avoided. Three, extraneous tissue at the periphery of the gland is removed. The hilum of the spleen is carefully dissected, and the splenic artery and vein are transected and tied by suture ligature. The stapled mesenteric vasculature is oversewn. Fourth, the gland should be tested for vascular integrity. Using a syringe with a tapered connector attached, ice cold preservation solution should be carefully instilled into the common iliac artery and the gland carefully examined from all aspects for evidence of preservation solution extrusion. These should be identified and ligated.

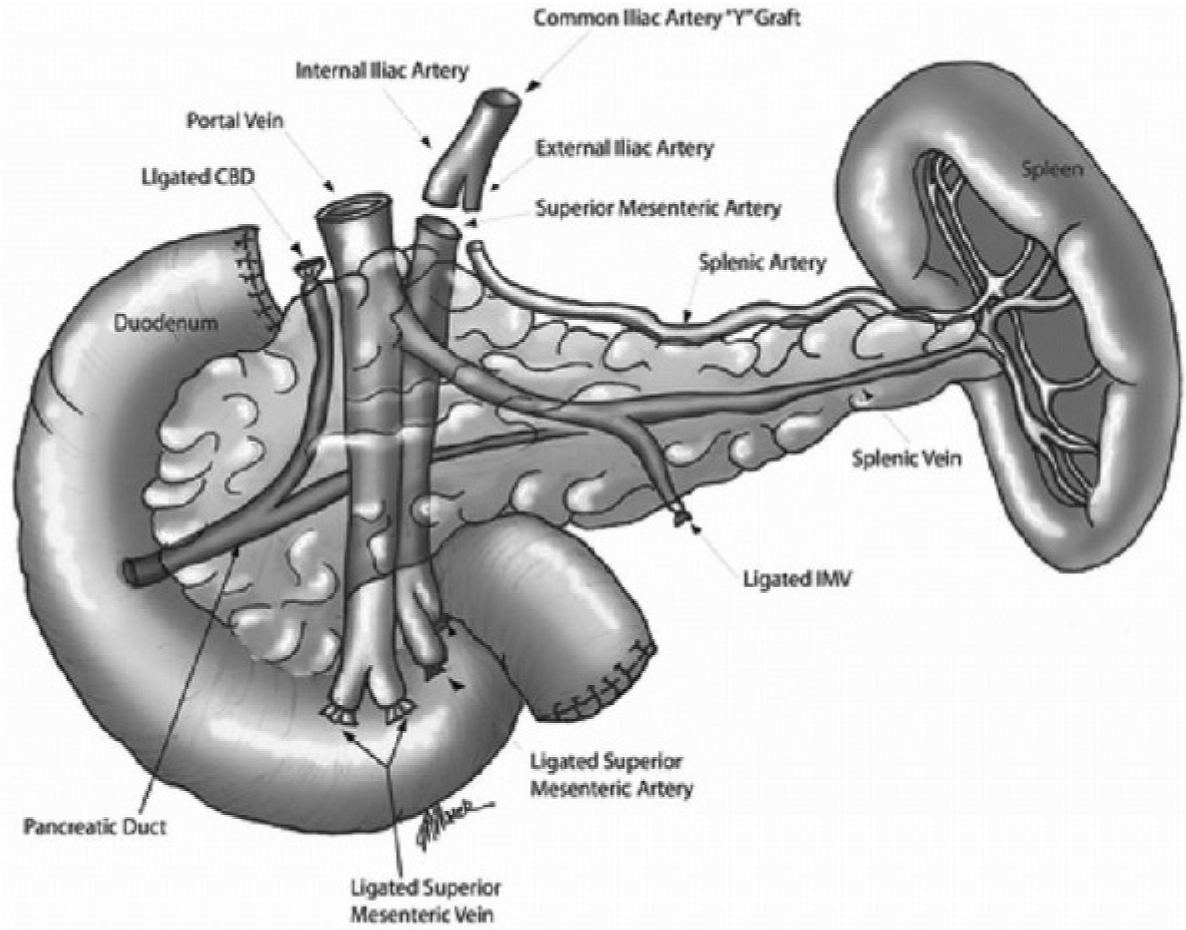


PLATE 15.1 Anatomy of procured pancreatic allograft before backbench preparation. CBD, common bile duct; IMV, inferior mesenteric vein. (From Lipshutz GS, Wilkinson AH. Pancreas-kidney and pancreas transplantation for the treatment of diabetes mellitus. Endocrinol Metab Clin North Am 2007;36:1015-1038, with permission. see color image)

Surgical Implantation Techniques

The main surgical controversies regarding pancreatic transplantation techniques have involved the method of exocrine drainage and vascular drainage. To provide the mass of islets needed to produce insulin and treat diabetes, it is necessary to transplant both the exocrine and endocrine pancreas. During the initial development of pancreas transplantation, procedures including duct ligation and creation of a duodenal button to drain exocrine secretions were tested but were fraught with complications, and these methods in general have been abandoned. Many studies and much interest have been focused on the handling of the exocrine pancreatic secretions. The most commonly used techniques today are enteric drainage and bladder drainage. This situation may change if pancreatic islet transplantation becomes a readily available clinical reality.

Enteric Versus Bladder Drainage

Enteric drainage of the exocrine pancreas into the small intestine is the most physiologic approach for drainage of exocrine secretions. The whole pancreas, together with a segment of donor duodenum, is transplanted with a side-to-side anastomosis to the recipient's small bowel (Plate 15.2). It has become the most popular of the drainage options, with more than 80% of SPK operations and more than 50% of PAK transplantations and PTA performed by this method. Some centers still prefer bladder drainage in PAK transplantation and PTA (due to higher rates of pancreatic allograft rejection in these two groups) in order to monitor serial urine amylase in the evaluation of rejection, whereas this method of monitoring is lost with enteric drainage.

Bladder drainage of highly alkaline pancreatic secretions with high concentration of amylase can result in fluid and electrolyte abnormalities (volume contraction, metabolic acidosis) and urologic abnormalities (cystitis, urethritis, balanitis, and reflux pancreatitis) that can have a major impact on postoperative morbidity and quality of life. It is largely for these reasons that the bladder drainage technique has been replaced by enteric drainage. The major danger associated with enteric drainage is the risk for development of a duodenoenteric leak, typically occurring in the early postoperative period, which may lead to graft loss and intra-abdominal sepsis. The danger of a duodenal leak may be somewhat less when the anastomosis is to the bladder, and the leak can sometimes be managed conservatively by bladder catheterization.

Few centers now choose bladder drainage as their primary method of exocrine drainage. When they do, pancreatic allografts are typically transplanted with a side-to-side pancreatic duodenocystostomy (Plate 15.3). A disadvantage of such enteric drainage of exocrine secretions is the inability to monitor urinary amylase as a means of detecting pancreatic allograft rejection. With current immunosuppressive protocols, however, this disadvantage is a minor one.

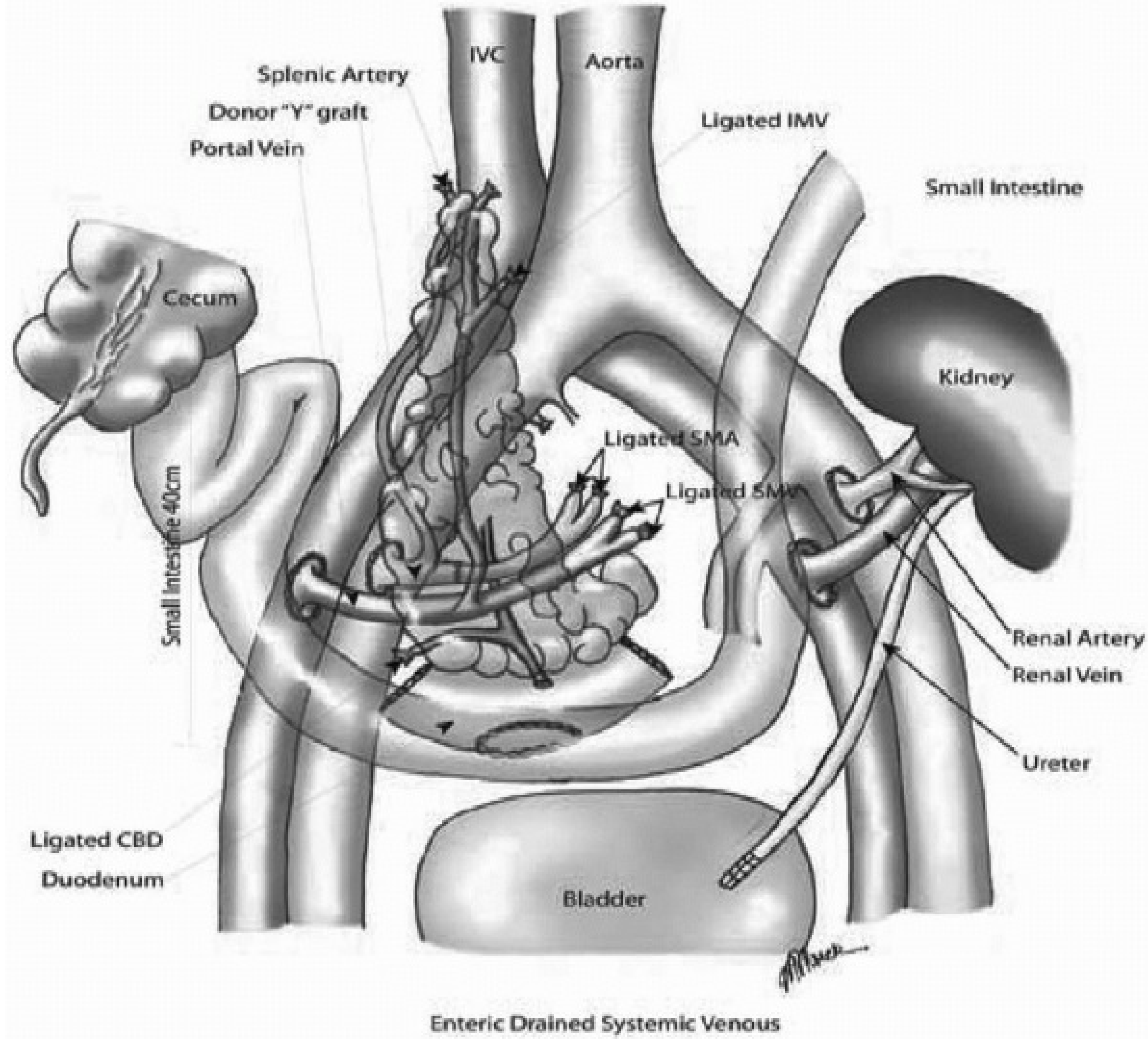


PLATE 15.2 Systemic venous and enteric-drained pancreatic allograft with kidney on the left. (From Lipshutz GS, Wilkinson AH. Pancreas-kidney and pancreas transplantation for the treatment of diabetes mellitus. Endocrinol Metab Clin North Am 2007;36:1015-1038, with permission. see color image)

Systemic Versus Portal Drainage

Most pancreatic allografts are transplanted heterotopically like kidneys in the pelvis using the iliac vasculature (Plates 15.2 and 15.3). Advantages of this approach include lower rates of allograft thrombosis, easier access for percutaneous biopsy, and the ability to use either the bladder or intestine for drainage of exocrine secretions. With systemic venous drainage, basal and stimulated peripheral serum insulin levels are 2 to 3 times higher than normal because insulin does not undergo first-pass hepatic effect. Patients may be susceptible to peripheral hyperinsulinemia with portal hypoinsulinemia and postprandial hypoglycemia, and some report that the high ambient insulin levels, insulin resistance, and abnormal lipoprotein metabolism may accelerate the

progression of atherosclerotic cardiovascular disease in recipients. Portal venous drainage (Plate 15.4) results in normal insulin levels with improvements in lipoprotein metabolism compared with systemic venous drainage. However, there are higher rates of allograft thrombosis, and percutaneous biopsy, when necessary, is more challenging. In addition, enteric drainage is required owing to cephalic placement of the donor duodenum.

Preoperative and Intraoperative Preparation

After the patient is admitted and a thorough history and physical examination are performed, blood draw including type and cross, chest radiography, and a 12-lead electrocardiogram should be performed. Some centers perform a bowel prep or series of enemas to clear the colon of formed stool. Leukocyte-reduced packed red blood cells should be prepared for the patient. Some centers administer a preoperative dose of aspirin (if the patient is not already receiving it) and an oral antifungal agent. Intraoperative immunosuppression should be ordered and prepared.

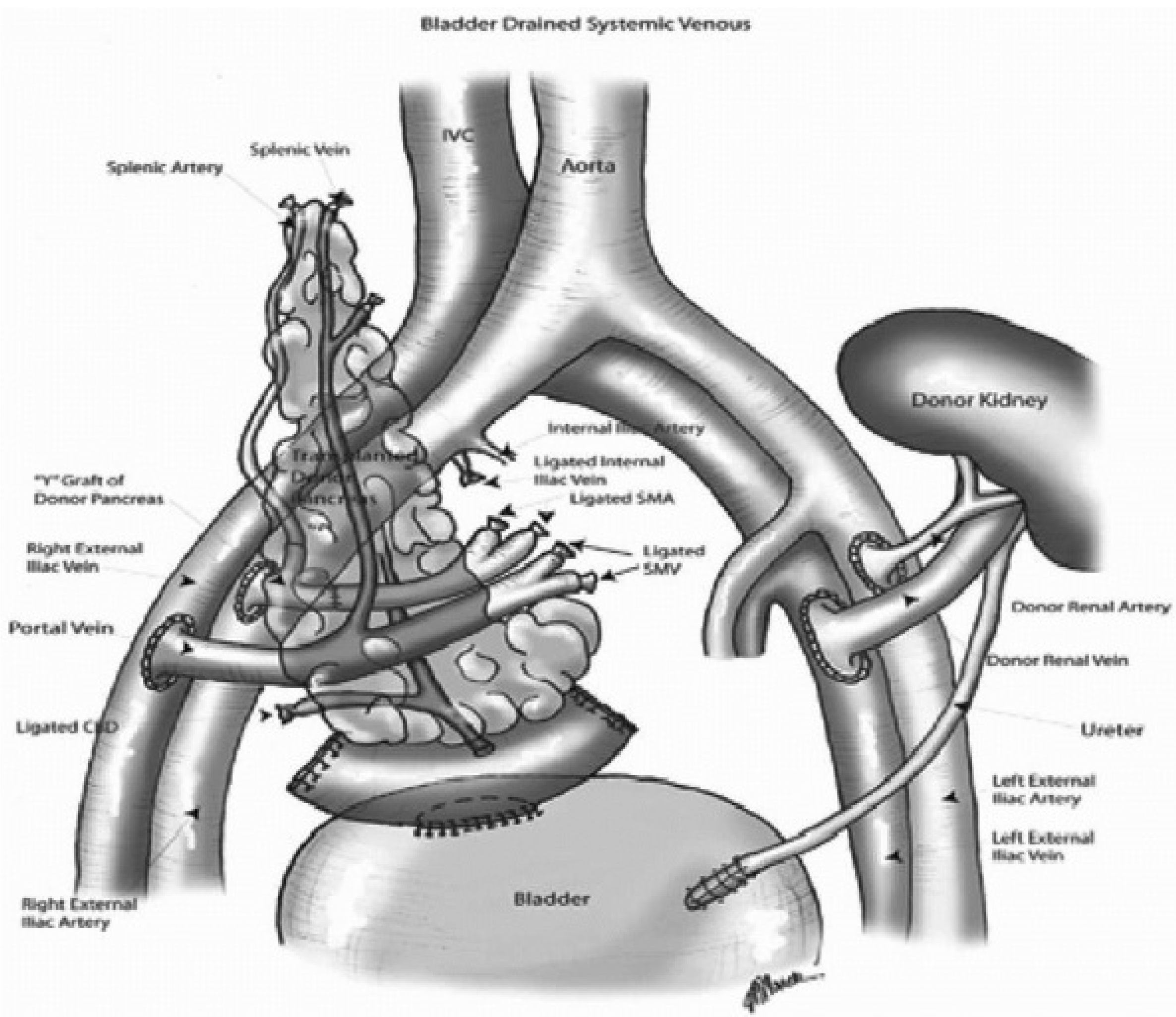


PLATE 15.3 Systemic venous and bladder-drained pancreatic allograft with kidney on the left. (From Lipshutz GS, Wilkinson AH. Pancreas-kidney and pancreas

transplantation for the treatment of diabetes mellitus. Endocrinol Metab Clin North Am 2007;36:1015-1038, with permission. see color image)

While awaiting the transplantation, half the normal dose of insulin should be administered, and serum glucose levels should not exceed 250 mg/dL because of concern for the development of acidemia intraoperatively, leading to intraoperative management difficulties. Preoperatively, blood glucose levels should be monitored every 4 hours and a sliding scale used for dosing regular insulin. Long-acting forms of insulin are avoided, allowing the surgeon to assess pancreatic allograft function in the operating room. Patients should undergo dialysis if there is significant evidence of volume overload or hyperkalemia.

Intraoperatively, patients generally have a nasogastric tube placed, and both arterial access and central venous access are obtained. Some centers have abandoned the routine use of nasogastric tubes. Poor gastrointestinal function may compromise absorption of immunosuppressive therapies, and many centers use intravenous induction agents, lessening the need for early gastrointestinal function to absorb oral immunosuppressants (see “Immunosuppression” below). Slow resumption of bowel function may follow transplantation, and, occasionally, prolonged nasogastric suctioning may be required in cases of a persistent ileus. A broad-spectrum antibiotic is administered (e.g., piperacillin/tazobactam) before skin incision.

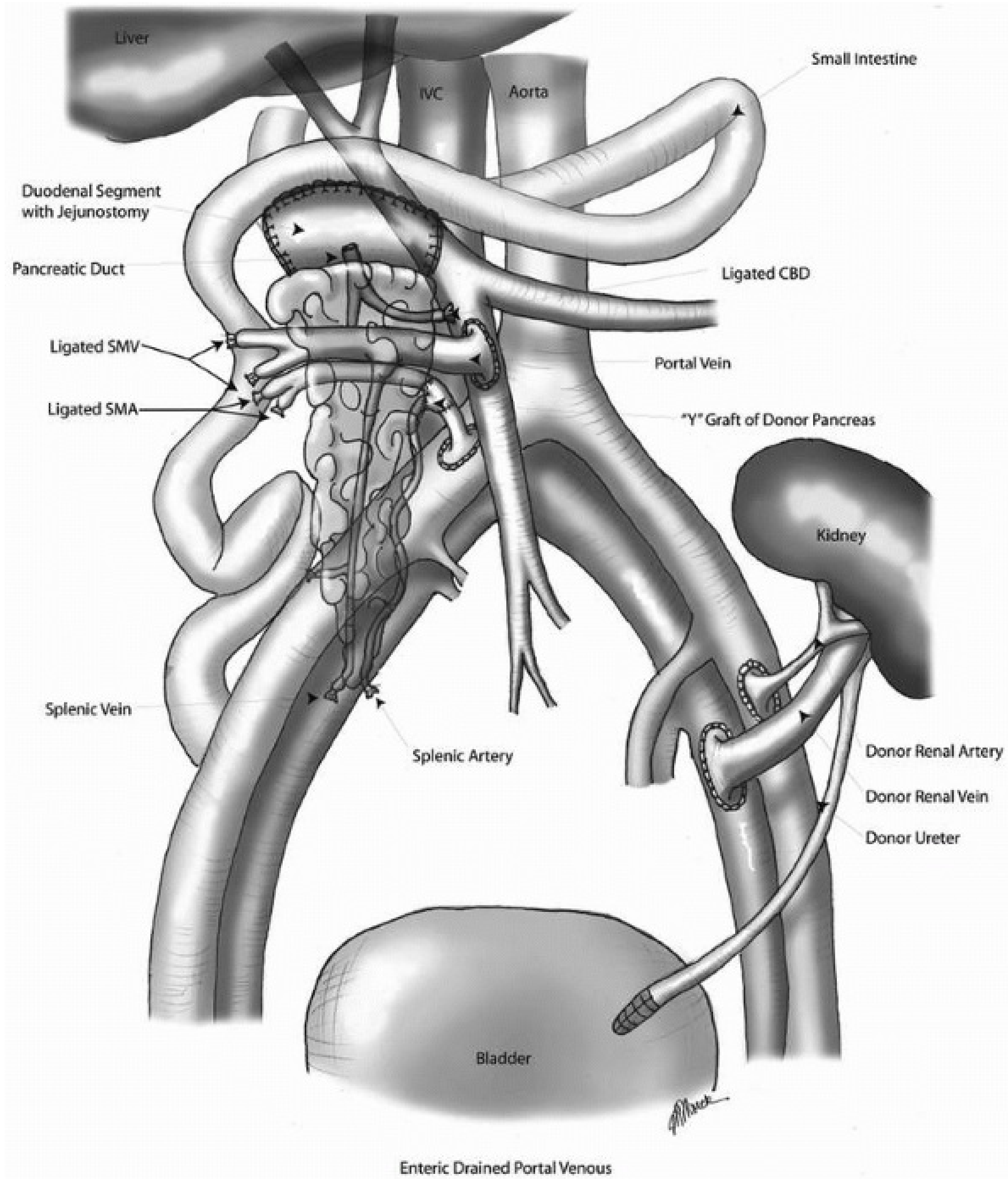


PLATE 15.4 Portal venous and enteric-drained pancreatic allograft with kidney on the left. SMA, superior mesenteric artery; SMV, superior mesenteric vein. (From Lipshutz GS, Wilkinson AH. Pancreas-kidney and pancreas transplantation for the treatment of diabetes mellitus. Endocrinol Metab Clin North Am 2007;36:1015-1038, with permission. see color image)

POSTOPERATIVE COMPLICATIONS

Unlike solitary kidney transplantation, in which the allograft is typically placed in a retroperitoneal location, pancreatic allograft placement is intra-abdominal. Because of the length of the operative intervention and the manipulation of the small intestine

and anastomosis (whether bladder or enteric drained), an ileus should be expected in the immediate postoperative period. Although studies have shown no significant difference in major postoperative complications in diabetic versus nondiabetic patients, especially with regard to wound complications, postoperative ileus, nausea, and vomiting are common after a pancreas transplantation. Because of the use of high-dose corticosteroids with induction agents at some centers, the need for frequent blood sugar monitoring is essential. Some centers use an insulin infusion in the immediate postoperative period. Others do not because following the serum or whole-blood glucose is important in assessing complications that may occur in the early postoperative period, particularly the possibility of allograft thrombosis.

Anastomotic Leak

Duodenal segment leaks in the bladder-drained pancreas recipient most often occur in the first 3 months after transplantation and usually present with the acute onset of abdominal pain and elevation of serum amylase. Diagnosis can be made by performing a cystogram or by nuclear medicine imaging. Treatment is nonoperative in as many as two thirds of patients, usually requiring prolonged Foley urethral drainage. Resistant cases may require exploration and closure of leakage site or enteric conversion.

The development of an anastomotic leak is the most serious complication of an enteric-drained whole pancreas transplantation. Leaks from enteric-drained pancreas transplants are suggested by the sudden onset of severe abdominal pain, rising serum amylase and creatinine levels, and fever. Early duodenal segment leaks tend to result from technical complications or as a result of ischemia. Late duodenal leaks tend to be due to rejection, infection, or ischemia of the duodenal staple line. Leaks do not result in alteration of endocrine function. However, patients present with elevated white blood cell counts, graft tenderness, and fever and generally lead to a pancreaticocutaneous fistula or peripancreatic abscess. These are particularly serious because of the spillage of succus entericus within the abdomen. Computed tomography (CT) and percutaneous drainage usually demonstrate a mixed infection of bacteria and often fungus. Broad-spectrum antibiotics are essential, and surgical exploration should be performed without delay. At laparotomy, a decision regarding the extent of the infection, its potential for clearance, and need for removal of the pancreatic allograft must be made. Treatment of the infection, if inadequate, will lead to organ failure, sepsis, and often death of the recipient. Some have converted the allograft to a Roux-en-Y limb when there has been evidence of an anastomotic leak; however, this has not always been successful in salvaging the allograft.

Graft Pancreatitis

Pancreatitis of the allograft is a common postoperative complication and can occur in a

variety of settings. It is usually self-limited and resolves early in the patient's postoperative course. Pancreatitis typically occurs as a result of cold ischemic storage and reperfusion injury or from handling during organ recovery. It usually induces a mild hyperamylasemia without significant clinical consequence, is self-limited, and resolves with conservative therapy. In more severe cases, significant ischemia-reperfusion injury can be the cause and can lead to allograft thrombosis, likely due to the effect on the vasculature. Doppler ultrasound studies are essential in evaluating graft dysfunction and an examination of the arterial waveforms will often demonstrate high resistive indices with sharp arterial peaks and poor runoff ("water-hammer" pulsations) (Fig. 15.5). Such poor runoff should raise concern of impending allograft thrombosis. In addition to heparinization, some have suggested that octreotide may be effective in improving this condition.

For bladder-drained pancreas transplants, reflux pancreatitis of urine has been described. It is most common in patients with distended neurogenic

---

bladders. It is managed by encouraging more frequent urination, Foley drainage, or self-catheterization to avoid high urinary residuals. α_1-Adrenergic receptor blocking agents such as terazosin may be useful in some. Patients with persistent reflux pancreatitis should undergo enteric conversion.

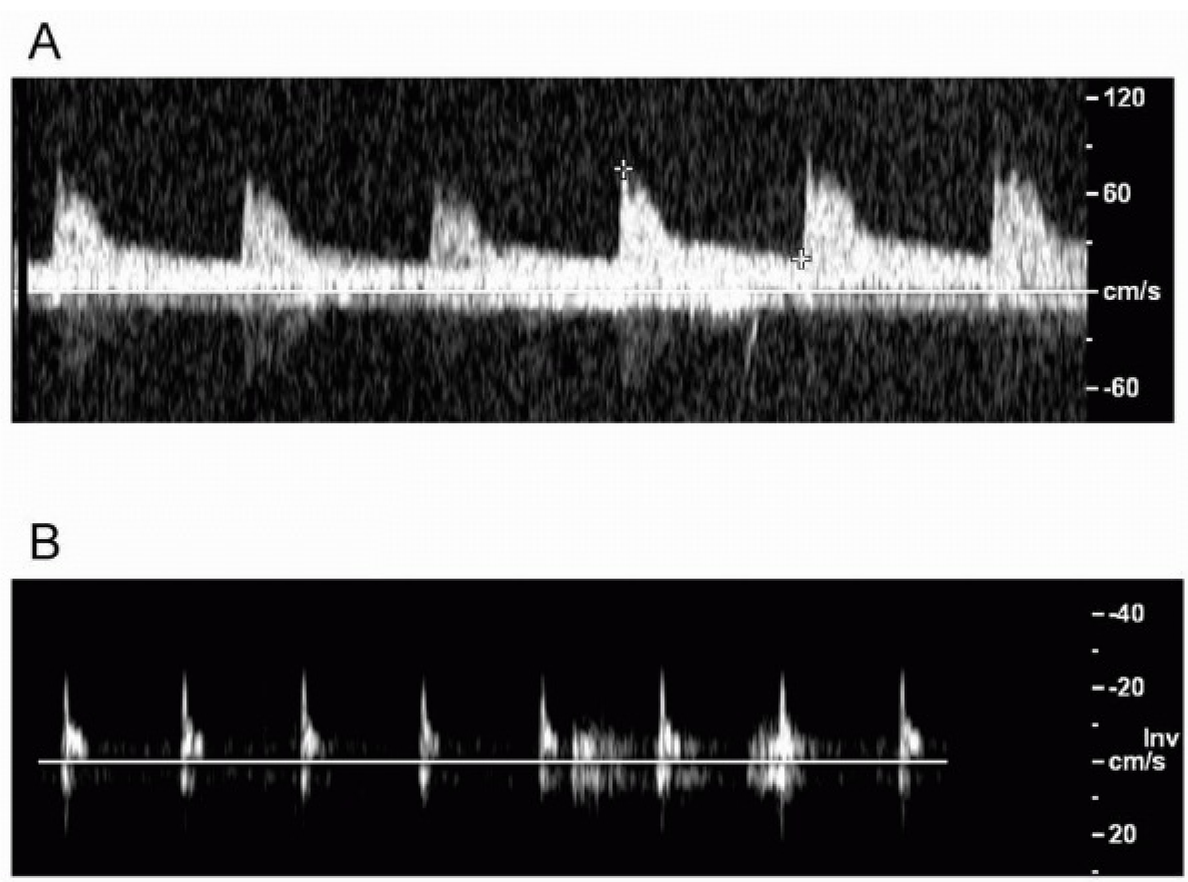


FIGURE 15.5 A: Normal arterial waveform with low resistive index and good runoff in the splenic artery of a pancreatic allograft. **B:** "Water-hammer" pulses are

demonstrated in this Doppler waveform indicating a high resistive index and poor runoff. Note the relative absence of diastolic flow.

Thrombosis

Graft thrombosis is well recognized and the most common early cause of loss of a pancreatic allograft. It is a devastating complication that can occur in as many as 10% to 20% of pancreatic transplant recipients. Most graft thromboses occurs in the first week after transplantation. Both donor and recipient factors increase the risk for thrombosis. Recipient factors are ones that decrease blood flow to the allograft and include pancreatitis, hypotension, acute rejection, and reperfusion injury. Donor factors include older age (>45 years), longer cold ischemia times, and donor death due to a cerebrovascular event.

Thrombosis of a pancreatic allograft may occur in either the arterial or the venous system. Arterial thrombosis may occur in the splenic artery or superior mesenteric artery; it sometimes occurs in both. Arterial thrombosis of the superior mesenteric artery leads to nonviability of the duodenal segment. On exploration, the pancreas appears soft and pale. In general, early on the patient feels no abdominal pain, and there is typically an acute rise in serum glucose with a fall in serum amylase. Even in the face of a patent splenic artery, surgical removal is generally the most appropriate measure because loss of the superior mesenteric arterial blood supply will leave the duodenal segment compromised. In some cases, the most distal end of the superior mesenteric artery or splenic artery may thrombose because these vessels become end arteries and have no outflow at the distal end. Although thrombosis at these locations initially may result in a transient hyperamylasemia, if imaging demonstrates good perfusion of the allograft, these distal thromboses will likely be of no long-term consequence (Fig. 15.6). However, long-term antiplatelet agents would be recommended.

Venous thrombosis usually presents with graft swelling, resulting in symptoms of abdominal pain. Serologically, patients demonstrate a rise in glucose and amylase. On abdominal exploration, the graft often appears enlarged, dark blue, and engorged. Doppler ultrasound examination is routinely used to examine vascular flow. In the case of venous thrombosis, there is high resistance in the pancreatic arteries with no flow in the pancreatic veins. Pancreatectomy is required.

Prevention and postoperative vigilance are the main measures for addressing the risk for allograft thrombosis. Anticoagulation and antiplatelet drugs are the main measure to prevent graft thrombosis; however, with this, the risk for postoperative bleeding increases. Doppler ultrasound imaging (alternatively CT angiography or magnetic resonance angiography) should be employed for any indication of early graft

dysfunction.

Gastrointestinal Bleeding

Early gastrointestinal bleeding may occur in either the bladder-drained or enteric-drained pancreas transplant recipient. This is typically due to bleeding from the suture line of the duodenal-ileal anastomosis or the duodenal-bladder anastomosis. Causes include ischemia-reperfusion injury of the duodenal mucosa or a bleeding vessel at the suture line of the anastomosis. When heparin or antiplatelet agents are used to decrease the risk for allograft thrombosis postoperatively, bleeding can be evident by either a fall in the hematocrit or the development of melenic stool. In addition, in uremic patients who have a delay in kidney allograft function, platelet dysfunction may become evident, and bleeding can occur. In both cases, bleeding tends to stop with cessation of anticoagulation, or transfusion of packed red blood cells and platelets in the case of uremia and delayed kidney function. Bleeding in enteric-drained patients usually resolves with such therapy. However, in bladder-drained patients, bladder irrigation may be necessary, and cystoscopy may be required to remove larger clots. Occasionally, open cystotomy may be necessary with fulguration or ligation of a bleeding vessel.

Abscess and Infection

Intra-abdominal infections are much more common after pancreas transplantation than after kidney transplantation alone and represent a significant cause of mortality if not adequately treated. Peripancreatic fluid collections can become infected, and conservative therapy with percutaneous drains and intravenous antibiotics is often adequate (Fig. 15.7). However, persistence or lack of resolution will require consideration of operative exploration and drainage. Pancreatectomy must be considered in these situations. A dangerous and often late complication in patients with peripancreatic abscesses is the development of a mycotic aneurysm and serious and life-threatening bleeding.

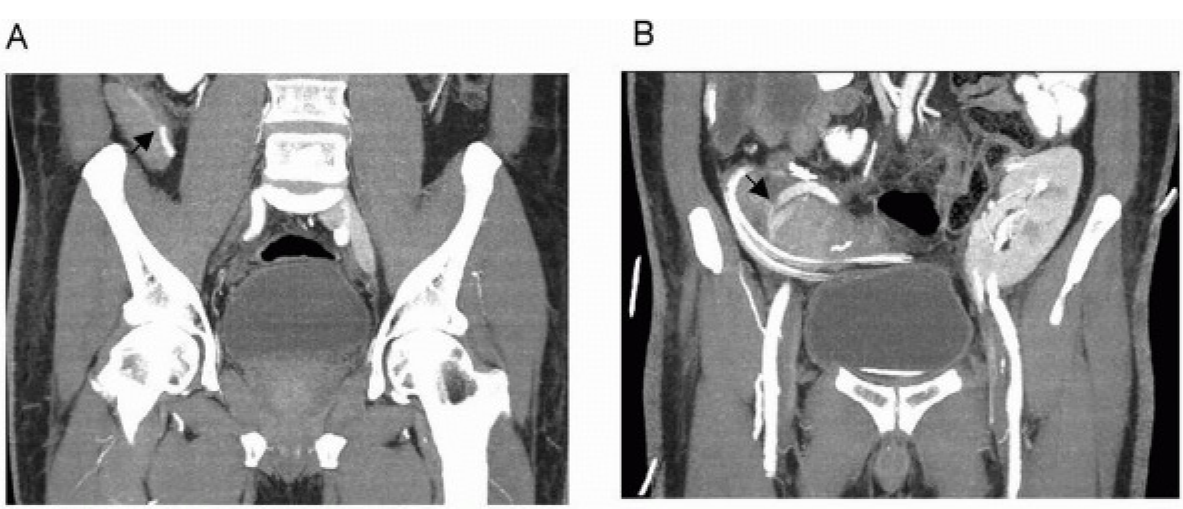


FIGURE 15.6 Computed tomographic angiogram of pancreatic allograft. *Arrow* demonstrates thrombosis of distal splenic artery (A) and distal SMA superior mesenteric artery of the allograft. Note that the gland is well perfused because of collateral blood flow.

Neurogenic Bladder and Urinary Tract Infections

Neurogenic bladder is a frequent complicating factor after transplantation. Urinary tract infections are also more common in diabetic recipients because of the higher incidence of a neurogenic bladder. Chronic intermittent self-catheterization may be necessary in some patients to completely evacuate the bladder. This can be challenging in some owing to vision loss. Prophylaxis with daily trimethoprim-sulfamethoxazole or ciprofloxacin is recommended.

Orthostatic Hypotension

Orthostatic hypotension with supine hypertension is a common result of autonomic neuropathy and may be transiently exacerbated after successful transplantation, particularly if the patient was in a fluid-positive state before transplantation. This condition can be challenging to treat on an outpatient basis. Initial treatment is to recommend increased salt intake in the diet; salty soups and bullion are recommended. If ineffective, patients should be prescribed sodium bicarbonate, up to 1300 mg taken orally 4 times daily, and fludrocortisone acetate (Florinef), 0.1 to 0.2 mg daily, should be added. Most patients respond to this form of therapy, and over time (typically many months later), fludrocortisone can be weaned and discontinued, and sodium bicarbonate doses can be decreased. If this is ineffective, midodrine (an α-adrenoreceptor agonist), up to 10 mg taken orally 3 times a day, can be added. In some, this may be poorly tolerated because supine hypertension often occurs, resulting in severe headaches. Clonidine can improve orthostatic hypotension, probably by a peripheral venoconstricting effect. Orthostatic hypotension typically resolves as the hematocrit rises; this process can be expedited with erythropoietin injections or packed red blood transfusions if necessary.

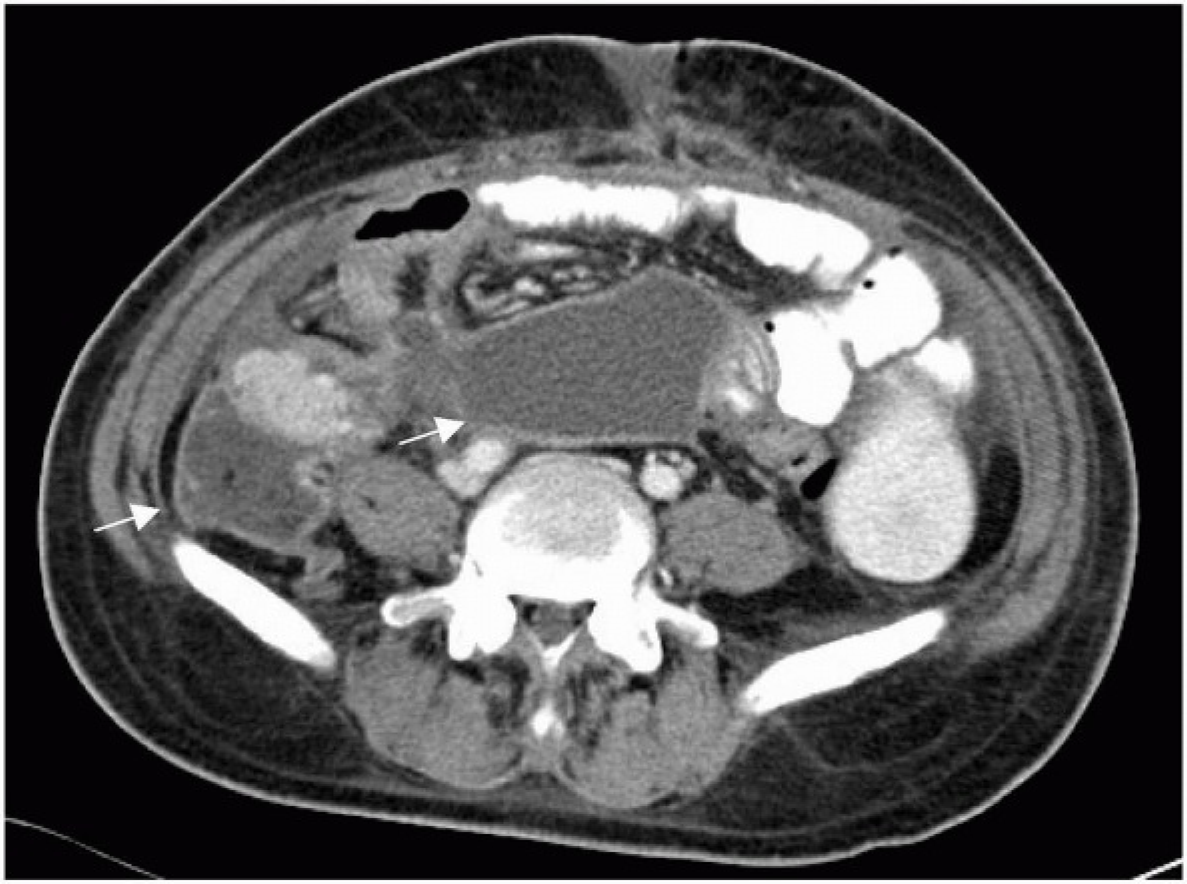


FIGURE 15.7 Computed tomography demonstrates peripancreatic fluid collections.

Allograft Rejection

Chronically elevated glucose is a poor sign and is a late finding in allograft rejection. It usually implies that the rejection has been ongoing for some time. The diagnosis of pancreas allograft rejection can be difficult to make and can only be confirmed with a percutaneous biopsy. Pancreatic allograft rejection is generally heralded by a rise in the serum amylase, not glucose. In effect, the exocrine pancreas and a rise in serum enzymes are used as a surrogate to diagnose rejection. The islets, in the initial phases of rejection, are spared, and serum glucose remains normal. Only later, when inflammation and destruction of the islets have occurred, does hyperglycemia result. Patients will at times report an acute rise in home monitoring of whole blood glucose after long periods of not checking their glucose. However, it is likely that allograft rejection began a significant amount of time earlier and that, only at that time, when the glucose was checked, was hyperglycemia detected. At this stage, rejection is usually irreversible. Rejection must be recognized early, before the development of hyperglycemia, to prevent complete destruction of islet tissues.

In SPK transplantation, the kidney allograft often shows clinical signs of rejection first before the pancreatic allograft. This is heralded by an acute rise in the serum creatinine such that a kidney biopsy is prompted. Although it is possible to have

pancreatic without kidney allograft rejection when recipients have received organs simultaneously and from the same donor, it is very uncommon, probably occurring in less than 5% of cases. Thus, when possible, a kidney biopsy should be employed first to determine the cause of graft dysfunction to prevent unnecessary immunosuppression in these patients. A percutaneous kidney biopsy is generally considered a safer procedure for patients because of the intra-abdominal location of the pancreatic allograft and the greater risk for postprocedure hemorrhage. If this is not diagnostic or does not show rejection in the face of elevated pancreatic exocrine enzymes, a pancreatic allograft biopsy should be performed. This is generally performed under ultrasound or computed tomographic guidance. If possible, any antiplatelet agents should be discontinued before biopsy.

The diagnosis of rejection in PAK and PTA transplantation is much more challenging. A rise in serum amylase or lipase could indicate rejection or another nonspecific process. Urine collection for amylase and examination for urinary eosinophils are useful in bladder-drained pancreas transplants. This requires that urinary amylase was followed at routine outpatient visits. However, in these cases, diagnosis also requires a percutaneous biopsy or a transcystoscopic biopsy of the head of the pancreas. Such difficulty in diagnosis in these groups may in part explain their overall worse graft survival compared with SPK recipients and why some centers continue to use bladder drainage in both PAK and PTA patients.

Treatment of pancreatic allograft rejection generally requires antibody therapy (typically, antithymocyte globulin; see Chapter 5) which should, ideally, not be given unless rejection is biopsy proved. A high-dose steroid pulse (5 mg/kg), while often causing an initial decline in serum amylase and lipase, may be followed by rebound rejection because this therapy alone is not effective or long lasting.

Immunosuppression

Immunosuppressive therapy for whole-organ pancreas transplantation with SPK is not markedly different than that for kidney transplantation alone. One-year rates of rejection have steadily decreased and are currently in the 10% to 20%

---

range depending on the type of transplantation and immunosuppressive regimen. Nearly all recipients receive some form of antibody induction, with 65% receiving maintenance therapy with a tacrolimus-mycophenolate mofetil combination.

Because of the frequency of acute rejection episodes in SPK transplantation, there is a tendency by most centers to be more aggressive with chronic immunosuppression protocols employed typically as triple immunosuppression postoperatively. Although the combination of tacrolimus, mycophenolate mofetil, and prednisone is the most common post-transplantation regimen, some centers have developed protocols with steroid withdrawal or are steroid free. Some centers have employed sirolimus in their maintenance regimen. Limited data with a tacrolimus-sirolimus combination have

shown excellent short-term outcomes, but attempts to date, except in a few selected cases, of calcineurin inhibitor avoidance or minimization have been overall less successful. In general, maintenance of higher levels of calcineurin inhibitors in pancreas transplant recipients is recommended compared with kidney alone patients.

PAK and PTA recipients are thought by some to be at higher risk for allograft rejection than SPK recipients. This is likely in part explained by not having an HLA-matched kidney present that can be evaluated to help determine the status of the pancreatic allograft. Typical regimens in these patients are based on triple immunosuppression. Some studies with steroid withdrawal and the use of sirolimus in these patients have suggested inferior results.

OUTCOME OF PANCREAS TRANSPLANTATION

There are significant complexities in comparing survival probabilities between ESRD patients who undergo different and subsequent renal replacement therapies. Caution is advised in comparing transplant and dialysis groups because they are not strictly comparable; those with the least severe manifestations of diabetes are more likely selected for transplantation of the pancreas, whereas those with morbid manifestations and severe secondary complications are often declined. This is reflected in multiple studies regarding the benefit or detriment of pancreas and renal transplantation versus renal transplantation alone in this patient population. Although both primary and repeat kidney transplantations have been shown to provide greater survival benefit in diabetic patients compared with nondiabetic patients, there have been conflicting reports regarding whether SPK provides additional survival benefit over renal transplantation alone.

Data from the U.S. Scientific Renal Transplant Registry supplemented with data from the U.S. Renal Data System indicate that SPK recipients can expect to live 15 years longer than type 1 diabetic patients who were not transplanted and remain on the waitlist. In addition, recipients of an SPK can expect to live 10 years longer than if they were a type 1 diabetic recipient of a deceased donor kidney alone. Overall, the projected extra lifetime gained for all SPK recipients is 23 years; those in the cohort of 18 to 29 years of age are projected to gain as many as 49 years, whereas those 40 to 49 years of age are expected to gain 19 years. The overall adjusted mortality rates for SPK, living kidney recipients, and deceased donor recipients were 40, 41, and 59 deaths per 1000 patient-years. The results of this analysis suggest that there is a survival advantage with pancreas transplantation for all demographic subgroups except those 50 years or older at the time of transplantation.

With this increased survival, however, there is the additional risk for excess initial morbidity and mortality, primarily related to the procedure itself and the risk for early complications (Table 15.1). In this same study, SPK recipients had a two-fold increased risk for death after transplantation. In addition, their overall risk for mortality was higher after transplantation. When compared with waitlist type 1 diabetic patients

receiving dialysis, it takes about

100 days for SPK recipients to reach the same relative mortality risk (mortality risk immediately after transplantation is >1.3). This is nearly twice as long as recipients of deceased donor kidneys only (43 days) and 7 times as long as those receiving a living donor kidney (15 days). However, despite this early elevated mortality risk with SPK transplants, with the selection criteria in use today and the current post-transplantation management, diabetic recipients can expect improved longevity with transplantation.

TABLE 15.1 Overall Mortality Risk Among Patients with Type 1 Diabetes Mellitus According to Method of Renal Replacement Therapy

Treatment	Days to Equal Risk	Days to Equal Survival	Five-Year Relative Risk
Dialysis (waitlist or reference)			1.0
Simultaneous pancreas and kidney	101	170	0.40
Living donor	15	72	0.45
Deceased donor	43	95	0.75

Modified from Ojo AO, Meier-Kriesche HU, Hanson JA, et al. The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. Transplantation 2001;71:82-90.

EFFECT OF PANCREAS TRANSPLANTATION ON DIABETIC COMPLICATIONS

The goal of kidney and pancreas transplantation in diabetic recipients is to restore renal function, normalize carbohydrate metabolism, and establish a state of normoglycemia while improving quality of life. Successful transplantation is not only life enhancing but also life saving. It frees patients from exogenous insulin and dietary restrictions and the emotional burden that these carry. Quality-of-life improvements include a greater satisfaction with life, a feeling of control and independence, and improved perceptions of both physical and mental health. Although the value of making patients insulin independent is clear, the value of arresting and sometimes reversing secondary complications of chronic diabetes mellitus is not and continues to be evaluated.

Nephropathy

Studies have demonstrated that renal allografts transplanted into diabetic recipients demonstrate signs of diabetic nephropathy as early as 2 years after transplantation. Thickness of the glomerular basement membrane has been compared between diabetic recipients of an SPK and diabetic recipients of only a kidney transplant. The thickness was found to be within the normal range in all SPK recipients, whereas it was increased in most diabetic kidney-alone recipients. Although these investigations have limitations, these studies suggest that when patients have prolonged normoglycemia, the recurrence of diabetic glomerulopathy is prevented.

Other studies at 5 and 10 years in PTA patients demonstrate that there was no amelioration of established diabetic nephropathy lesions 5 years after pancreas transplantation. However, after 10 years, there was reversal of diabetic glomerulopathy in patients with functioning pancreatic allografts. Glomerular and tubular basement membrane width, which was unchanged after 5 years, decreased after 10 years, falling into the normal range for some. Kimmelstiel-Wilson nodular lesions disappeared, and glomerular capillaries previously compressed by mesangial expansion were noted to have reopened in some patients.

In comparing the renal outcome of recipients of SPK and of isolated deceased donor kidney transplants, it must be recalled that the kidney quality of SPK donors tends to be better than that of kidney donors alone. It is this improved quality that is largely responsible for the improved renal outcome of SPK recipients. Patients often request a pancreas transplant in order to “protect” their kidney transplant. Although this is an intuitively logical request, it is important to remind patients that it remains the quality of the kidney, rather than the presence of a functioning pancreas, that is most likely to

determine outcome.

Cardiovascular Disease

Whether cardiovascular disease (CVD) risk improves or worsens after pancreas transplantation is an important outcome measure because CVD is the most common cause of mortality in patients with diabetes. Hyperlipidemia and other risk factors should be aggressively treated in diabetic transplant recipients, particularly in the presence of coronary artery disease. Improvement in glucose levels reduces risk for microvascular complications in type 1 diabetes mellitus. However, there are few prospective studies with a large number of patients examining the relationship between the re-establishment of normoglycemia in long-term diabetic patients and a reduction in cardiovascular mortality.

In general, studies do suggest a cardioprotective effect of normoglycemia established after successful pancreas transplantation. A greater decrease in left ventricular mass and normalization of diastolic dysfunction has been shown in SPK recipients compared with those who underwent kidney transplantation alone. Progression of coronary artery disease, using mean segment diameter loss on coronary angiography, was less in those with a functioning graft after SPK than in those with pancreatic graft failure. Carotid artery disease also appear to progress less with SPK than with kidney transplant alone. Vascular disease events and mortality are likely to be less after pancreas transplantation.

Retinopathy

Many studies have examined the impact of pancreas transplantation on existing diabetic retinopathy. Most studies have shown little impact. Recipients with severely impaired vision may note some improvement, although some patients with pre-existing severe disease may progress to blindness. Longer-duration studies in patients with less advanced retinopathy and in those who have macular edema have suggested there may be some improvement with pancreas transplantation. In some with preproliferative retinopathy, stability or regression after transplantation was detected, and macular edema improved. However, the improvement in macular edema and subsequent mild visual improvement may in fact be related to a return of normal fluid balance provided by the kidney allograft.

Neuropathy

Focal neuropathies and polyneuropathies are common complications of diabetes mellitus. They affect both the autonomic and somatic nervous systems. Polyneuropathy is disabling, is the most common neurologic complication of diabetes, and is a contributor to foot ulceration. As with other secondary complications of diabetes, extended observation periods may be necessary to recover from the pathologic abnormalities that developed over the previous 20 or more years since the onset of

diabetes mellitus in these patients.

Prospective studies of patients with polyneuropathy demonstrate a general trend toward improvement in the motor and sensory nerve conduction studies at 1 year and in autonomic function at 5 years. Patients who had either PTA or

an SPK or PAK transplantation showed improvement throughout a 10-year follow-up period, demonstrating that the effect was not solely related to correction of uremia. Diabetic autonomic nervous system dysfunction is associated with mortality. Some data suggest that patients with moderate neuropathy, but not those with severe neuropathy, who retained a functioning pancreas transplant had longer survival than those whose pancreatic function was lost. Of those who died during the period of observation, the results of cardiovascular autonomic testing correlated with mortality.

QUALITY OF LIFE

Multiple studies have reported a better quality of life in pancreas transplant recipients than in diabetic patients who are recipients of a kidney alone. Patients indicate satisfaction with diet flexibility and health management after pancreas transplantation. They are relieved of the strict dietary restrictions and the emotional burden of frequent blood sugar monitoring and insulin therapy. A significantly higher proportion of recipients of a pancreas transplant are working compared with patients on the waiting list. However, social and diabetes-related worries may persist, partly because a large number of recipients have advanced diabetic end-organ damage such as retinopathy and neuropathy by the time they receive the pancreas transplantation.

Despite these anticipated benefits, it is critical that patients have a realistic and educated understanding of the relative risks and benefits of the range of transplant and nontransplant options available to them. Patients and family members may tend to overestimate the benefits and underestimate the risks of the procedures they are facing. It is difficult to quantitate the sense of liberation felt by lifetime diabetic patients who no longer must self-inject insulin and monitor every morsel they eat. Permitting patients that hope, while educating them as to what is involved in achieving it, is at the core of successful pancreas transplantation.

CHOICE OF PROCEDURE

Patients and their physician advocates may be faced with a difficult dilemma when choosing between a kidney transplantation alone and an SPK transplantation. This dilemma is reflected in the ongoing discussions on this topic in the medical and transplantation literature. SPK transplantation is associated with increased early morbidity but may offer better long-term quality of life and the greater potential for stabilization or improvement of diabetic complications. Most centers recommend kidney transplantation alone when a live donor is available because this option offers the best long-term patient and graft survival; a PAK transplantation may follow.

Patients choosing between SPK and cadaveric kidney transplantation must be thoroughly informed regarding the comparative risks and benefits of the two procedures and, in particular, must have realistic expectations regarding the effect of pancreas transplantation on secondary complications. Patients should also be aware of the fact that, in most regions of the United States, the waiting time for an SPK transplant is about one third of that for a cadaveric transplant alone, and that a prolonged period of dialysis may expose them to additional risk. Patients seeking an isolated pancreas transplant in the presence of normal or near-normal renal function (PTA or PAK) should be made aware that some data suggest a relative survival disadvantage of this procedure. This survival disadvantage is likely a reflection of the excellent survival of diabetic patients whose renal function is good. The rationale to proceed with an isolated pancreas transplantation should be based on the judgment that quality of life will be improved and the survival disadvantage outweighed by avoiding the need for insulin.

TRANSPLANTATION OF PANCREATIC ISLETS

Transplantation of the islets of Langerhans is an appealing alternative to whole-organ pancreas transplantation, primarily because of the lowered risk for surgical complications. Recall that the pancreas is predominantly an exocrine gland and that clusters of endocrine cell, the islets, are scattered throughout the gland. These islets contain the glucose-responsive, insulin-secreting β cells. The autoimmune destruction of these β cells is the cause of type 1 diabetes mellitus. Replacement of the β-cell mass provides the freedom from insulin therapy enjoyed after successful pancreas transplantation, and the exocrine pancreas is unnecessary for insulin independence. Separation of the islets from the exocrine pancreas allows transplantation with minimally invasive techniques. More importantly, islet transplantation does not require vascular and allograft duodenal anastomoses, thus avoiding the major sources of surgical complications.

Until recently, success with islet transplantation has been poor compared with whole-organ pancreas transplantation. The results of more than 400 islet transplantations performed up to 1998 showed insulin independence in only 8% of recipients at 1 year, compared with 80% or more of pancreas transplant recipients. The so-called Edmonton protocol (see Shapiro and colleagues in “Selected Readings”) generated new optimism for the success of islet transplantation. Using a steroid-free immunosuppression protocol (based on sirolimus, tacrolimus, and daclizumab), insulin independence was achieved in a small group of type 1 diabetic patients, without renal failure, receiving islet transplants alone. The recipients selected for this trial suffered hypoglycemic unawareness or “metabolic instability.” The investigators transplanted the islets immediately after isolation, using a radiologically guided, transhepatic portal venous infusion technique. Besides the steroid-free immunosuppression, the success of the Edmonton protocol clearly depended on transplantation of an adequate islet mass, and

this often necessitated multiple transplants with islets isolated from two to four donors. Since the original publication of this protocol, several other programs have reported similar experience, and up to 80% of patients have been reported to remain insulin independent after 2 years. The 5-year follow-up from the Edmonton program has been somewhat disappointing. The median duration of insulin independence was 15 months, and only 10% of the completed transplant recipients remained insulin independent at 5 years. C-peptide secretion was maintained in 80% of patients, however, and these patients required only half the pretransplantation daily dose of insulin and showed less glucose lability than before transplantation.

Current Status

The knowledge, expertise, and expenses required to isolate a large number of quality human islets for transplantation are substantial. The U.S. Food and Drug Administration (FDA) deems isolated human islets for transplantation a biologic product and currently requires an approved Investigational New Drug application and Institutional Review Board approval for investigators conducting clinical islet transplantation research. The FDA also requires that investigators isolating human islets for transplantation use current Good Manufacturing Processes (cGMPs), such as clean room facilities, careful record keeping, and quality controls. Islet transplantation thus remains an experimental technique and is yet to become part of the routine diabetes care.

Islet Isolation

Fundamental steps in the process of islet isolation are procurement of the donor pancreas, transportation to the isolation laboratory, enzymatic digestion of the glandular tissue, separation, and purification of the islets. In most

laboratories, it may take one to four donor pancreata to yield enough islets for investigators to consider the mass adequate for a recipient. In the case of a patient who requires three transplants, for example, it may take as many 12 donor pancreata to provide persistent insulin independence. The preferential allocation of pancreata from the best donors to whole-organ transplantation may explain the multiple organs required to provide adequate islets.

Improved transplant success may result from post-isolation culture of the islets for up to 72 hours before transplantation, and this may permit insulin independence with a single donor transplant. The culture period may improve success by providing the time to measure the viability of the islets, time that is not available with immediate transplants. It is not clear whether the culture actually decreases the number of isolations required per recipient. Careful recipient and donor selection may also be a factor allowing single donor success.

Recipient Selection

Like other allografts, islet transplant recipients require immunosuppression to prevent rejection. Therefore, patients are selected for clinical trials based on the risks of immunosuppression compared with ongoing insulin therapy for diabetic control. As with whole-organ pancreas transplantation, more recipients who received islets before the Edmonton protocol received a renal transplant either before or simultaneously with the islet transplant. For these patients, there is a minimal additional risk for immunosuppression for the islet transplant beyond that required for the renal transplant. For this reason, investigators continue to enroll type 1 diabetic patients with renal failure in clinical trials of islet-after-kidney and simultaneous islet-kidney transplantation.

For islet transplantation alone in nonuremic patients, investigators look for life-threatening, or at least severe, problems with blood glucose control to balance the risks of immunosuppression. Hypoglycemic unawareness is a readily documented indication. “Metabolic instability” is a less precise inclusion criterion for clinical trials, but a limited number of fully compliant patients working diligently with an attentive diabetologist clearly manifest this severe problem.

Future Directions

For the near future, it is likely that islet transplantation will remain a procedure that is limited in its scope. Enthusiasm for its promotion has been dampened somewhat by the disappointing long-term results. Transplantation tolerance, eliminating the need for long-term immunosuppression, might allow patients to undergo islet transplantation earlier in the course of their disease, providing improved quality of life, and lowering the risk for long-term complications. Encapsulation of the islets within a device that bars the immune response, for example, by preventing recipient immune cells from contacting the islets, is an enticing means to achieve tolerance but has met with limited success to date. At the time of this writing, information for professionals and patients about current clinical trials is available at http://www.isletservice.org.

Selected Readings

American Diabetes Association. Pancreas and islet transplantation in type 1 diabetes. Diabetes Care 2006;29:935.

Aull-Watschinger S, Konstantin H, Demetriou D, et al. Pre-transplant predictors of cerebrovascular events after kidney transplantation. Nephrol Dial Transplant 2008;23:1429-1435.

Bromberg J, LeRoith D. Diabetes cure-is the cup half full? N Engl J Med 2006;23:1429-1435.

Fernandez LA, Turgeon NA, Odorico JS, et al. Superior long-term results of simultaneous pancreas-kidney transplantation from pediatric donors. Am J Transplant 2004;4:2093-2101.

Gruessner AC, Sutherland DE. Pancreas transplant outcomes for United States (US) and non-US cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of June 2004. Clin Transplant 2005;19:433-455.

Gruessner RW, Sutherland DE, Gruessner AC: Mortality assessment for pancreas transplants. Am J Transplant 2004;4:2018-2026.

Humar A, Kandaswamy R, Granger D, et al. Decreased surgical risks of pancreas transplantation in the modern era. Ann Surg 2000;231:269-275.

Humar A, Ramcharan T, Kandaswamy R, et al. Technical failures after pancreas transplants: why grafts fail and the risk factors—a multivariate analysis. Transplantation 2004;78:1188-1192.

Larsen JL, Colling CW, Ratanasuwan T, et al. Pancreas transplantation improves vascular disease in patients with type 1 diabetes. Diabetes Care 2004;27:1706-1711.

Leichtman A, Cohen D, Keith D, et al. Kidney and pancreas transplantation in the United States, 1997-2006: The HRSA Breakthrough Collaboratives and the 58 DSA Challenge. Am J Transplant 2008;8:946-957.

Nathan DM. Isolated pancreas transplantation for type 1 diabetes: a doctor's dilemma. JAMA 2003;290:2861.

Ojo AO, Meier-Kriesche HU, Hanson JA, et al. The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. Transplantation 2001;71:82-90.

Ryan EA, Paty BW, Senior PA, et al. Five-year follow-up after clinical islet transplantation. Diabetes 2005;54:2060.

Shapiro AM, Ricordi C, Hering BJ, et al. International trial of the Edmonton protocol for islet transplantation. N Engl J Med 2006;355:1318.

Venstrom JM, McBride MA, Rother KI, et al. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA 2003;290:2817-2823.

Young B, Gill J, Huang E, et al. Living donor kidney versus simultaneous pancreas-kidney transplant in type 1 diabetes: an analysis of the OPTN/UNOS database. Clin J Am Soc Nephrol 2009;4:845-852.

16

Kidney Transplantation in Children

Eileen W. Tsai

Robert B. Ettenger

Kidney transplantation is universally accepted as the therapy of choice for children with end-stage renal disease (ESRD). About two thirds of pediatric patients with ESRD ultimately receive a kidney transplant. Successful transplantation in children and adolescents not only ameliorates uremic symptoms but also allows for significant improvement of delayed skeletal growth, sexual maturation, cognitive performance, and psychosocial functioning. The child with a well-functioning kidney transplant can enjoy a quality of life that cannot be achieved by any form of dialysis therapy.

Current success in pediatric renal transplantation is attributed to improvements in transplantation technology, immunosuppressive therapy, and the provision of age-appropriate clinical care. Transplantation continues to result in better survival than dialysis for pediatric patients of all ages. Five-year survival rates in transplant patients are close to 95%, whereas in dialyzed patients, the survival rates are about 80%. Nevertheless, success in pediatric kidney transplantation remains a challenging undertaking. Children and adolescents are constantly growing, developing, and changing. Each developmental stage produces a series of medical, biologic, and psychological challenges that must be appropriately addressed if truly successful graft outcome and rehabilitation are to be realized.

Much of the statistical data reviewed in this chapter comes from databases that have provided an invaluable resource for the advancement of pediatric transplantation. These databases have enabled the evaluation and extrapolation of data from multiple pediatric renal transplant programs that tend to be small when compared with their adult counterparts. Major databases referred to are the *North America Pediatric Renal Transplant Cooperative Study* (NAPRTCS), the *Scientific Registry of Transplant Recipients* (SRTR), and the *United States Renal Data System* (USRDS) annual report (see websites).

EPIDEMIOLOGY OF END-STAGE RENAL DISEASE IN CHILDREN

Incidence

The incidence and prevalence of treated pediatric ESRD have been increasing since 1989. As of 2005, the incidence rate of new cases of ESRD in children up to 19 years of age was 15 per 1 million U.S. children per year. The point prevalence of ESRD in this population is 80 per 1 million U.S. children. The incidence of ESRD increases with age, with the highest incidence observed in children between 15 and 19 years of age (28 per million). Adolescents represent approximately 50% of treated pediatric ESRD patients.

There is a wide variation by ethnic group in the incidence rates of treated ESRD. African American children have the highest incidence rate of 27 per 1 million, as compared with 12 per 1 million white children, 15 per 1 million Asian and Pacific Islander children, and 17 per 1 million Native American children. The incidence is higher in African Americans across all age groups but is most prominent in the 15- to 19-year-old age group (60 per 1 million African Americans compared with 20 per 1 million whites). During the past 20 years, incident rates for white pediatric patients have remained constant. For African American patients and other nonwhite ethnicities, however, the rates of ESRD have more than doubled. The incidence of glomerulonephritis as a cause of ESRD is up to 3 times higher in African American pediatric patients than in white pediatric patients; there is no racial predilection for other causes of pediatric renal disease. Patients with focal segmental glomerulosclerosis (FSGS) make up almost 23% of all pediatric African American dialysis patients and more than 30% of adolescent African American dialysis patients. Boys have higher incidence of treated ESRD than girls in all age groups.

Etiology

Congenital, hereditary, and cystic diseases account for about 50% and glomerular diseases for 20% of cases of pediatric ESRD (Table 16.1). Incidence rates for patients with glomerular diseases and patients with congenital, hereditary, and cystic diseases continue an upward trend.

The most common primary diagnoses remain aplastic, hypoplastic, or dysplastic kidney and obstructive uropathy, each present in about 16% of patients. FSGS is the third most common (12%) and continues to be the most prevalent acquired renal disease. In contrast to adults, ESRD caused by diabetes mellitus or hypertension is rare in children.

Access to Transplantation

Between 1987 and 2007, more than 9,500 children received 10,400 transplants in the United States. At the time of transplantation, about two thirds of pediatric recipients of kidney transplants are older than 12 years, 17% are 6 to 12 years of age, 17% are between the ages of 2 and 5 years, and less than 1% are younger than 1 year of age. About 60% are male, 61% are white, 17% are African American, and 16% are Hispanic.

Pediatric transplantations constitute 4% to 7% of all kidney transplantations in the United States. The number of pediatric kidney transplantations has remained relatively constant during the past decade at about 800 each year. During the same period, the number of adult kidney transplantations has increased by nearly 50% (see Chapter 1, Fig. 1.1). Historically, the number of living donor transplants consistently exceeded the number of deceased donor transplants in pediatric ESRD. As of 2005, the number of pediatric kidney deceased donor transplants exceeded living donor transplants, following the trend found in adults. The number of deceased donor transplants increased from 278 in 2000 to 468 in 2005. This trend is likely a result of changes made to the United Network for Organ Sharing donor allocation policy, whereby children receive priority for deceased donor kidneys from donors younger than 35 years (see Chapter 4).

Children continue to represent only a small percentage of the national waiting list for deceased donors. During the past decade, their number has remained constant in the range of 500 to 650, whereas the adult list has more than doubled in number. Additionally, median waiting times have decreased in pediatric patients. In 2005, the median waiting time for all pediatric groups was less than 300 days. This compares favorably with the latest data on median waiting time in adults, which during the past 10 years was never less than 920 days in any age group. This difference reflects kidney allocation rules that are specifically designed to favor children because of their unique needs for growth and development.

TABLE 16.1 Incidence of End-Stage Renal Disease in Pediatric Transplant Patients According to Primary Disease, 2007*

Primary Renal Disease	Incidence (%)
Cystic, hereditary, and congenital disease	**47.4**
Renal hypoplasia, dysplasia	16.0
Congenital obstructive uropathy	15.6

Polycystic disease	3.0
Medullary cystic disease (nephronophthisis)	2.8
Prune belly syndrome	2.6
Congenital nephrotic syndrome	2.6
Alport syndrome, other familial disease	2.2
Cystinosis	2.1
Oxalosis	0.5
Glomerulonephritis (GN)	**21.3**
Focal segmental glomerulosclerosis	11.7
Chronic GN	3.4

Membranoproliferative GN type I	1.8
Idiopathic crescentic GN	1.8
IgA nephropathy	1.3
Membranoproliferative GN type II	0.9
Membranous nephropathy	0.4
Interstitial nephritis, pyelonephritis	**7.1**
Chronic pyelonephritis, reflux nephropathy	5.3
Interstitial nephritis	1.8
Secondary GN, vasculitis	**6.2**
Hemolytic uremic syndrome	2.7
Systemic lupus erythematosus	1.5

Henoch-Schbönlein purpura	1.2
Wegener granulomatosis	0.5
Other systemic immunologic disease	0.3
Hypertension	**1.3**
Miscellaneous conditions	**1.3**
Neoplasms	1.0
Sickle cell nephropathy	0.2
Diabetes mellitus	0.1
Other	**9.4**
Uncertain etiology	**6.0**

*The study included 9506 patients younger than 21 years.

Modified from the NAPRTCS 2007 annual report available at www.emmes.com/study/ped.

Timing of Transplantation

Renal transplantation should be considered when renal replacement therapy is indicated. In children, dialysis may be required before transplantation to optimize nutritional and metabolic conditions, to achieve an appropriate size in small children, or to keep a patient stable until a suitable donor is available. Many centers prefer that a recipient weigh at least 8 to 10 kg, both to minimize the risk for vascular thrombosis and to accommodate an adult-sized kidney. In infants with ESRD, a target weight of 10 kg may not be achieved until 12 to 24 months of age. At some centers, transplantation has been successful in children who weighed less than 10 kg or who were younger than 6 months.

Preemptive transplantation (i.e., transplantation without prior dialysis) accounts for 25% of all pediatric renal transplantations. The major reason cited by patients and families for the decision to undertake preemptive transplantation is the desire to avoid dialysis. Candidates for preemptive transplantation should have careful psychological assessment before transplantation because there may be a greater tendency for noncompliance in children who have not experienced dialysis. Nevertheless, there appears to be no impairment in graft outcome in pediatric recipients who have undergone preemptive transplantation when compared with those who have undergone dialysis before transplantation, and some data suggest a small improvement in allograft outcome. The reasons for the improved graft survival are unknown. Because of the waiting time for deceased donors, most preemptive kidney transplants are from living donors.

Patient and Graft Survival

Both patient and graft survival rates have improved steadily since systematic recording began in 1987. Patient survival after transplantation remains superior to that achieved by dialysis for all pediatric age groups. The overall 1- and 5-year patient survival rates are now 98% and 94%, respectively, for all primary transplants, and are marginally better for recipients of living donors than for deceased donors. The 1- and 5-year patient survival rates for living donor recipients are 98% and 96%, whereas those for deceased donor recipients are 97% and 93%. Although patients younger than 2 years of

age have lower survival rates, the situation has significantly improved within the past decade. Infection accounts for 29% of deaths. Other causes include cardiopulmonary disease (15%), malignancy (11%), and dialysis-related complications (3%). About 47% of patients who die do so with a functioning graft.

Graft survival rates for pediatric transplants are somewhat better than for adult transplants. One- and 5-year graft survivals are 95% and 85%, respectively, for living donor recipients and 93% and 77%, respectively, for deceased donor recipients. Of the more than 10,000 pediatric kidney transplantations performed since 1987, about 26% have failed. Chronic rejection accounts for 40% of graft failures, with acute rejection accounting for 9%. Other causes include vascular thrombosis (8%), recurrence of original disease (8%), and patient noncompliance (6%). Chronic rejection remains the most common and ever-increasing cause of allograft failure. Although some causes of graft failure, such as recurrence of the original disease, have remained constant during the past 10 years, loss from acute rejection and graft thrombosis has decreased. Technical issues remain a challenge and are a more common cause of graft loss in children than in adults.

PROGNOSTIC FACTORS INFLUENCING GRAFT SURVIVAL

The following factors are important determinants of the improving graft survival reported in pediatric patients. Long-term renal function is a particularly important consideration in pediatric renal transplantation because of its impact on post-transplantation skeletal growth.

Donor Source

Short- and long-term graft and patient survival rates are better in recipients of living donor transplants in all pediatric age groups. Younger transplant recipients benefit the most from living donor transplantation and enjoy a 20% to 30% better graft survival rate 5 years after transplantation. Shorter cold ischemia time, better human leukocyte antigen (HLA) matches, lower acute rejection rates, and better preoperative preparation help to account for the improved

---

outcome. During the past decade, however, marked improvement has been made in deceased donor patient and graft survival. These results may be related to temporal trends in immunosuppressive drugs, decreased transfusion requirements, and decreased use of young deceased donors.

Recipient Age

The trend for younger children, especially those younger than 2 years of age, to have lower graft survival rates than older children has been reversed. Some studies even suggest that adult kidneys transplanted into infants, with immediate graft function, may have the longest half-lives of any type of kidney transplant. Pediatric recipients

younger than age 11 years who received living donor transplants now have 5-year graft survival rates that are similar to those of recipients in older age groups. The rates were 96% for infants younger than 1 year, 91% for children 1 to 5 years old, and 85% for children 6 to 10 years old. The results for deceased donor recipients are also better in this age group than in adults generally. Recipients 1 to 5 years of age have a 5-year graft survival rate of 75% and recipients 6 to 10 years of age have a 5-year graft survival rate of 72%.

On the other hand, the long-term graft survival rates in adolescents are not as good as those seen in younger children, even though the short-term outcome is similar. The 1- and 5-year graft survival rates for adolescent recipients of living donor kidneys are 94% and 77%, respectively. For deceased donor kidneys, the graft outcomes were 93% and 63%, respectively. Adolescents have the poorest 5-year results of any age group except for recipients 65 years and older. Higher rates of medication noncompliance, loss of medical insurance during transition to adulthood, and a high recurrence rate of FSGS, which is the most common acquired cause of ESRD in this age group, have all been cited as potential causes for the reduced long-term outcome.

Donor Age

For all deceased donor recipients, kidneys from donors 11 to 17 years of age provide optimal graft survival and function. This group is followed next by donors 18 to 34, 6 to 10, and then 35 to 49 years of age. Grafts from donors younger than 5 years fare more poorly, and grafts from donors older than 50 years fare most poorly. Although transplanted kidneys grow in size with the growth of the recipient, transplantation with deceased donor kidneys from donors younger than 6 years is associated with decreased graft survival. The 5-year graft survival rate for recipients of deceased donor kidneys from donors younger than 1 year of age is only about 59%, compared with 73% and 67% for recipients of grafts from donors 1 to 5 years of age and older than 6 years of age, respectively. Kidneys from donors 11 to 17 years of age have the best 5-year graft survival of about 75%. Children younger than 5 years receiving a kidney from a donor younger than 1 year have the highest relative risk for graft failure.

Ethnicity

African American ethnicity is associated with a worse outcome. Five years after transplantation, African American children have graft outcomes of 57% and 70% for recipients of deceased donor and living related donor kidneys, respectively. For white and Hispanic recipients, graft survival rates at 5 years are 74% and 66%, respectively, for recipients of deceased donor kidneys, and 84% for living donor grafts. African American children have not only poorer graft survival but also poorer renal function compared to other ethnic groups.

HLA Matching in Children

In pediatric transplantation, most living donor transplants come from parents. Long-term graft survival is best when the donor is a HLA-identical sibling.

When considering transplants from HLA haplotype-identical sibling donors, some studies suggest that there is improved outcome when donor and recipient share “noninherited maternal antigens,” as distinct from “noninherited paternal antigens” (see Chapter 3). Additionally, improved outcomes have been reported with sharing of HLA-DR antigens in living donor transplantation and sharing of HLA-B antigens in deceased donor transplantation, although the differences, if any, are small.

Presensitization

Repeated blood transfusions expose the recipient to a wide range of HLA antigens and may result in sensitization to these antigens, leading to higher rates of rejection and graft failures. The graft failure rate increases by up to 30% for recipients with more than five blood transfusions before transplantation compared with those who had fewer transfusions. Blood transfusions have become less common since erythropoietin became an integral part of ESRD therapy. Hemoglobin levels in children on dialysis are lower than levels in their adult counterparts, and there is support for more aggressive management of anemia to forestall transfusions. Sensitization may also result from rejection and failure of a previous transplant, and the 5-year graft survival rate for repeat deceased donor transplantations is about 13% lower.

Immunologic Factors

Immunologic parameters in younger children are different from those in adults and older children. Such differences include higher numbers of T and B cells, higher $CD4^+$-to-$CD8^+$ T-cell ratio, and increased blastogenic responses. These differences may account for the increased immune responsiveness to HLA antigens and may be partly responsible for the higher rates of rejection that have been observed in children. With improved understanding and management of immunosuppression in pediatric patients, these higher rates of rejection have been significantly ameliorated.

Technical Factors and Delayed Graft Function

Surgical kidney transplant techniques used in older children are similar to those in adults (see Chapter 8). Placement of the vascular anastomoses depends on the size of the child and the vessels. An extraperitoneal approach is usually accomplished with the venous anastomoses to the common or external iliac vein and the arterial anastomoses to the common or external iliac artery. These vascular anastomoses tend to be more cephalad than for adult transplants.

Small children present difficult operative challenges. The relatively large size of the graft may result in longer anastomosis times, longer ischemia time, and subsequently

higher rates of early graft dysfunction. When possible, the transplanted kidney is usually placed in an extraperitoneal location, although with very small children, the placement can be intra-abdominal. The aorta and inferior vena cava are usually used for anastomoses to ensure adequate blood flow, but smaller vessels may be used. Vascular anastomosis may be problematic in a child with a previous hemodialysis access placed in the lower extremities or with a previous kidney transplant. Children should be evaluated thoroughly before transplantation to identify any potential anastomotic difficulties. Unidentified vascular anomalies may lead to prolonged anastomosis times and subsequently higher rates of delayed graft function (DGF) and graft thrombosis.

Occasionally, native kidney nephrectomy is necessary at the time of transplantation. Although this can be done routinely in living donor transplantations in which there is little cold ischemia time, it is preferable to avoid this, when possible, in recipients of deceased donor transplants. Native nephrectomy at

the time of transplantation prolongs the surgical procedure and may complicate fluid management and contribute to an increase in DGF.

DGF is discussed in detail in Chapter 9. It occurs in about 5% of living donor and 17% of deceased donor transplants and is associated with a reduced graft survival. In children with DGF, the 3-year graft survival rates are reduced by up 25%. Risk factors for DGF in children are more than five prior blood transfusions, prior transplantation, native nephrectomy, African American ethnicity, and a cold ischemia time of longer than 24 hours.

Antibody Induction

Antibody induction, with either polyclonal or monoclonal antibodies, is used either for prophylaxis against rejection or in a sequential manner to avoid nephrotoxicity resulting from early use of calcineurin inhibitors (see Chapter 5). The NAPRTCS database shows a nearly 17% reduction in the proportional hazard of graft loss with the use of antibody induction in living related transplantation, but surprisingly no significant survival advantage for deceased donor transplantation. Nevertheless, the use of induction agents continues to increase year by year. As a class, nondepleting antibodies (see Chapter 5) remain the most commonly used induction agents for pediatric transplants in the United States, although there has been a steady increase in the use of rabbit antithymocyte globulin (Fig. 16.1).

Transplantation Center Volume

Transplant outcome in high-volume pediatric renal transplantation centers has been reported to be superior to that found in lower-volume centers. High-volume centers (defined as the performance of more than 100 pediatric transplantations

between 1987 and 1995) reported a lower incidence of graft thrombosis and DGF,

improved long-term graft survival, and more frequent use of antibody induction.

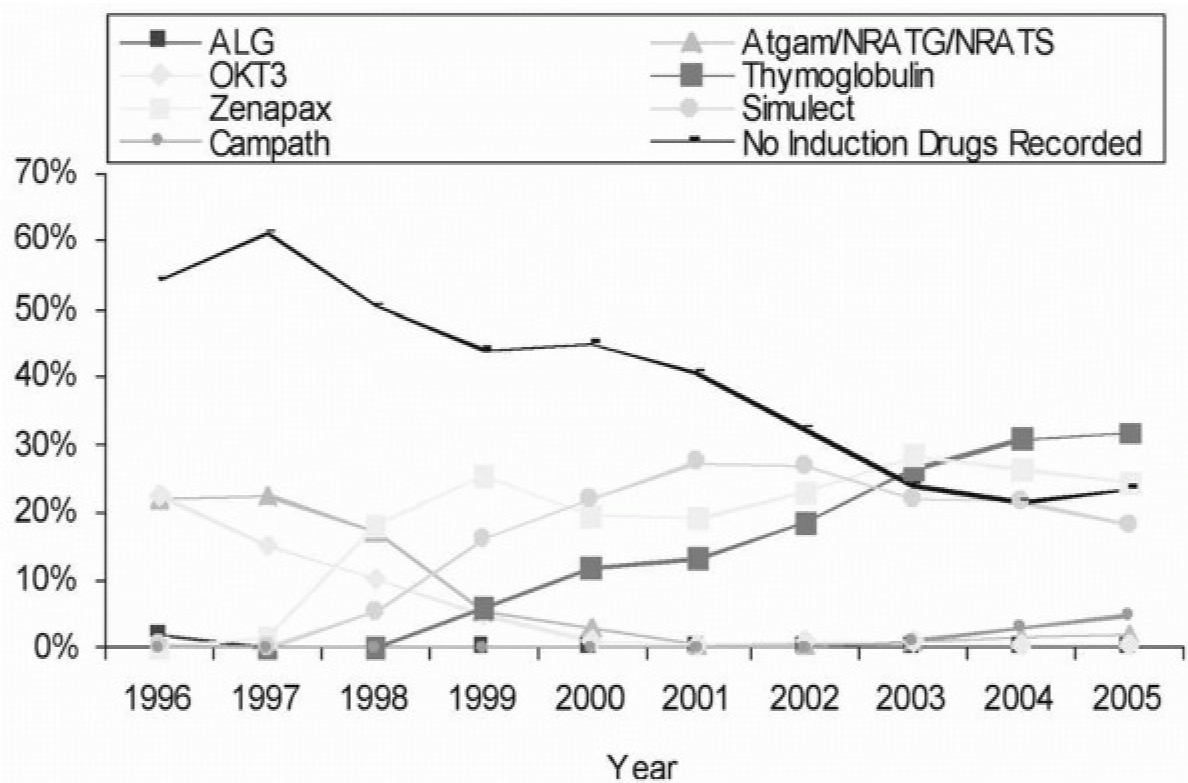


FIGURE 16.1 Immunosuppression use for induction for pediatric recipients with kidney transplants, 1996 to 2005.

Cohort Year

The results of pediatric renal transplantation have been steadily improving. The current 1-year and 5-year graft survival data represent up to 15% improvement during the past 20 years. Graft outcome in transplants from deceased donors performed between 1995 and 2006 is now equivalent to the graft survival in living donor transplantation performed between 1987 and 1994.

Recurrent Renal Disease in Pediatric Transplantation

Recurrent disease in the renal graft accounts for graft loss in almost 8% of primary transplantations and 10% of repeat transplantations. This is more than double that reported for adult transplantation. Both glomerular and metabolic diseases can recur, with most recurrences caused by glomerular disease.

Glomerular Diseases

Focal and Segmental Glomerulosclerosis

FSGS is the most common cause of graft loss as a result of recurrent disease. For patients whose original disease was steroid-resistant nephrotic syndrome or confirmed FSGS, the disease recurs in 30% to 40% of patients undergoing primary transplantation. When the first transplant was lost to recurrence, FSGS recurs in 70% to 85% of those undergoing subsequent transplantation. About 20% to 30% of transplants in patients with the diagnosis of FSGS fail because of recurrence. The mean time to graft failure from recurrence is 17 months.

Recurrence is usually characterized by massive proteinuria, hypoalbuminemia, and nephrotic syndrome with edema or anasarca and hypercholesterolemia. It may present immediately or weeks to months after transplantation. Predictors of recurrence include rapid progression to ESRD from the time of initial diagnosis (<3 years), poor response to therapy, younger age at diagnosis (but older than 6 years of age), Caucasian ethnicity, and the presence of mesangial proliferation in the native kidney. A protein permeability factor has been isolated from sera of patients with FSGS, and its concentration was found to correlate with recurrence and severity of disease in the transplanted kidney. The precise nature of this factor remains unclear, and there is no clinically approved assay to detect it.

Early post-transplantation recognition of recurrent FSGS is important because plasmapheresis (which may lower the serum levels of protein permeability factor) and high-dose calcineurin inhibitor may lead to significant reduction in graft losses because of recurrence. *In vitro* studies using rat glomeruli show that cyclosporine or tacrolimus, incubated with sera from FSGS patients, will inhibit the proteinuric effect of such sera. Thrice-daily cyclosporine administration may be used in doses that maintain high blood levels (see Chapter 5), and the dose is tapered slowly after achieving remission of the nephrotic syndrome and as cholesterol concentration decreases, or if significant toxicity develops. Some centers have used a high-dose continuous intravenous infusion of cyclosporine with similar improvement, or have used high-dose or thrice-daily administration of tacrolimus. Cyclophosphamide has also been reported to induce remission. Rituximab may prevent recurrence; however, results have been mixed, and its use is more successful in children than adults. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are used as adjuncts to decrease proteinuria. Plasmapheresis is generally

---

used with a frequency that matches disease severity and is occasionally required on a weekly basis for prolonged periods. Plasmapheresis, in combination with a high-dose calcineurin inhibitor, is reported to be superior to either when given alone. Although there is currently no consensus on the treatment regimen for FSGS, the protocol outlined in Table 16.2 represents a summation of our own experience. For deceased donor transplantation, recurrence is less in patients on high-dose cyclosporine and post-transplantation plasmapheresis. For living related transplantation, high-dose tacrolimus is effective when combined with more than five plasma exchanges.

Some studies report that living related donor transplant recipients suffer from a higher

rate of recurrence. The graft outcome in recipients of living donor grafts with FSGS recurrence is no better than the outcome observed in recipients of deceased donor grafts that have not experienced recurrence. These data have led some pediatric transplantation centers to reduce or discontinue the use of living related donation for patients with FSGS. However, the controlled settings of living donor transplantation may allow certain benefits in the event that FSGS does recur. The lower incidence of DGF in living donation may permit augmentation of the calcineurin inhibitor dose. In addition, the preplanning implicit in living donation permits preoperative and early postoperative plasmapheresis, an approach that may potentially prevent or decrease the severity of recurrent disease.

Alport Syndrome

Alport syndrome, or hereditary glomerulonephritis, is a progressive disease often associated with neurosensory hearing loss and ocular abnormalities such as anterior lenticonus and cataracts. The inheritance pattern can be X-linked, autosomal recessive, and autosomal dominant. The abnormality in almost all patients stems from mutations in the α_3, α_4, or α_5 helices of type IV collagen. In more than 80% of patients, Alport syndrome results from mutations in the *COL4A5* gene on the X chromosome.

Strictly speaking, Alport syndrome itself does not recur; however, antiglomerular basement membrane (anti-GBM) glomerulonephritis occurs in about 3% to 4% of patients after transplantation and can lead to graft loss. The antibodies causing the anti-GBM nephritis are usually directed against the α_5 chain

of the noncollagenous portion of type IV collagen in the GBM, but antibodies against the α_3 chain have also been described. The risk appears to be greatest in patients with mutations of *COL4A5* that prevent synthesis of the α_5 chain.

TABLE 16.2 Focal Segmental Glomerulosclerosis Protocol at the Mattel Children's Hospital at UCLA

- Identify the high-risk patient
- Living related donation if possible (to allow pretreatment and to avoid acute tubular necrosis so that high-dose cyclosporine or tacrolimus can be used)

- All patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as tolerated
- Living donor graft recipients
  - Ten pretransplantation plasma exchanges (1.5 volumes with albumin; fresh-frozen plasma for patients who are coagulopathic)
  - Three post-transplantation plasma exchanges (may need to be extended)
  - Tacrolimus 2 or 3 times daily; aim for trough levels of 12 to 15 ng/mL
- Deceased donor graft recipients
  - Ten post-transplantation plasma exchanges
  - May need to extend the number of plasma exchanges
  - Cyclosporine 3 times daily; aim for trough levels of 200 to 500 ng/mL

Anti-GBM glomerulonephritis presents as rapidly progressive crescentic glomerulonephritis with linear deposits of immunoglobulin G (IgG) along the basement

membrane and commonly leads to graft loss, with rates approaching 90%. It usually occurs within the first post-transplantation year. Asymptomatic cases with linear IgG deposits have also been reported. Treatment consists of plasmapheresis and cyclophosphamide, but such treatment is of only limited benefit. Retransplantation is associated with a high recurrence rate.

Membranoproliferative Glomerulonephritis

Histologic evidence of recurrence of membranoproliferative glomerulonephritis (MPGN) type I varies widely, with reported rates ranging from 20% to 50%. Clinical manifestations include proteinuria and deterioration of renal function. Risk factors for recurrence have been reported to include HLA-B8DR3, living related donation, and previous graft loss from recurrence. Graft loss occurs in up to 30% of cases. Histologic recurrence of type II disease occurs in virtually all cases, but graft loss is not inevitable and has been reported in up to 50% of patients. The presence of crescents in the native kidney biopsy and persistent proteinuria may predict severe recurrence that often leads to graft loss. There is no proven treatment for recurrence of MPGN in children. Anecdotal case reports describe success with high-dose corticosteroids, mycophenolate mofetil (MMF), or plasma exchange.

IgA Nephropathy and Henoch-Schönlein Purpura

Histologic recurrence with mesangial IgA deposits is common and occurs in up to 60% of patients with IgA nephropathy and in 35% of patients with HenochSchönlein purpura (HSP). Most of the recurrences are asymptomatic, but graft loss may occur, often associated with crescent formation. Data from adult centers suggest that a fulminant presentation of IgA nephropathy as the original cause of ESRD predicts poor outcome in the transplanted kidney with disease recurrence. In children, up to 10% of graft failures have been ascribed to recurrent IgA nephropathy or HSP. There is no effective therapy for the prevention or treatment of recurrent IgA nephropathy. Anecdotal reports that MMF administration prevents progression to graft failure have not been substantiated. ACE inhibitors and ARBs can be used for reducing proteinuria and preserving renal function.

Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS) accounts for up to 5% of primary renal disease in children leading to ESRD. In children, the most frequent form of HUS is diarrhea-associated (D+), or “typical,” and is caused by verocytotoxin-producing *Escherichia coli* (VTEC). Although this is the most common form of HUS in childhood, it results in ESRD in only 5% to 10% of cases. “Atypical” HUS is far less common in children. It is characterized by a prodrome that lacks diarrheal association (i.e., “D-”); it has a relapsing course and a very poor renal prognosis.

When considering transplantation in patients whose original cause of ESRD was HUS,

care must be directed to the form of HUS that the patient suffered. The diarrhea-associated, or typical, form does not usually recur after transplantation, whereas atypical HUS has a high propensity for recurrence. However, there are pitfalls in assessing recurrence of HUS. The D+/D- terminology can sometimes be misleading. Occasionally, patients with VTEC-associated HUS do not have diarrhea and therefore may be mistakenly labeled as D-. Similarly, diarrhea

---

disease can trigger HUS in a patient who is genetically predisposed to HUS and therefore erroneously is characterized as D+ HUS. In addition, it may be difficult to distinguish antibody-mediated vascular rejection from recurrent HUS, which presents histologically as thrombotic microangiopathy (TMA) (see Chapter 14). The calcineurin inhibitors may cause TMA in the transplanted kidney and produce a clinical picture that resembles HUS (see Chapters 5 and 9). Finally, other rarer causes of HUS in the post-transplantation patient may include use of valacyclovir; viral infections such as parvovirus, HIV and cytomegalovirus (CMV); and antibodies against the von Willebrand factor-cleaving metalloproteinase ADAMTS13. With these reservations in mind, it is reasonable to conclude that D+ HUS has a minimal recurrence rate, whereas the aggregate recurrence rate in D- HUS is 20% to 25%. The use of calcineurin inhibitors in both D- and D+ patients does not appear to trigger HUS recurrence, and avoidance of calcineurin inhibitors does not appear to prevent recurrence.

It has been recommended that at least 1 year of clinical quiescence occur before transplantation is attempted for patients with D- HUS, although this hiatus may not reduce the risk for recurrence. The prognosis is poor, with a 10% mortality rate and greater than 80% graft loss rate. For patients who have experienced recurrence, it is estimated that HUS will recur in about 50% of subsequent grafts.

Abnormal complement dysregulation has been associated with a severe form of D- HUS resulting in 60% disease recurrence and more than 90% graft failure. Patients have genetic defects in factor H, factor I, membrane cofactor protein (MCP), factor B, and C3. Pretransplantation genotyping for these mutations is recommended. Factor H deficiency or mutations that impair its function result in a state of continued complement activation with resulting low C3 and C4 levels. High-dose fresh-frozen plasma with plasma exchange has been advocated for this condition. Combined liver-kidney transplantation has been performed in a limited number of patients to restore normal circulating factor H with varying results.

An acquired factor H deficiency as a result of anti-factor H autoantibodies has been found in some children. Plasma exchange can be used to remove anti-factor H antibodies and immunosuppression with steroids and rituximab used to suppress further antibody production. Eculizumab, an anti-C5 monoclonal antibody, has successfully been used to treat D- HUS recurrence by decreasing the damage associated with anaphylatoxin C5a and preventing formation of membrane attack complex on cell surfaces. Randomized control trials of Eculizumab are in progress. Defects in factor I result in impaired protection of the endothelial surface against complement activation;

graft recurrence and survival rates are similar to those associated with factor H mutations. Defects in MCP, a transmembrane complement regulator that is highly expressed in the kidney, are associated with a much lower recurrence rate than defects in factor H or I. Transplantation of a kidney that expresses normal MCP should correct the defect. Defects in Factor B, which increase C3bBb convertase stability and result in permanent activation of the complement pathway, have been identified: there is little experience with their clinical management.

Living donor transplantation is not contraindicated for patients whose original disease was D+ HUS. On the other hand, living donor transplantation is not advocated for patients with D- HUS. This is because of the high recurrence rate in such patients. In addition, it has been noted that some parental carriers of D- HUS might not manifest the disease until later in life, and organ donation would put such carriers at excessive risk.

Antiglomerular Basement Membrane Disease

Anti-GBM disease is rare in children. A high level of circulating anti-GBM antibody before transplantation is thought to be associated with higher rate of

---

recurrence. Therefore, a waiting period of 6 to 12 months with an undetectable titer of anti-GBM antibody is recommended before transplantation to prevent recurrence. Reappearance of anti-GBM antibody in the serum may be associated with histologic recurrence. Histologic recurrence has been reported in up to half of cases, with clinical manifestations of nephritis in only 25% of these cases. Treatment for recurrence includes plasma exchange, cyclophosphamide, and corticosteroids. Graft loss is rare, and spontaneous resolution may occur.

Congenital Nephrotic Syndrome

Congenital nephrotic syndrome occurs in the first 3 months of life. It can be classified by mutations in the nephrin gene *(NPHS1),* podocin gene *(NPHS2),* or Wilms tumor suppressor gene *(WT1)*. Congenital nephrotic syndrome of the Finnish type (CNSF) is an autosomal recessive disease that occurs as a result of a mutation in the *NPHS1* gene. Although it is most commonly seen in Finnish patients, it is also found in other countries. The *NPHS1* gene is located on chromosome 19 and has as its gene product the protein *nephrin*. Nephrin is a transmembrane protein, which is a member of the immunoglobulin family of cell adhesion molecules. It is characteristically located at the slit diaphragms of the glomerular epithelial foot processes. Close to 100 mutations of *NPHS1* have been identified in CNSF, but more than 90% of all Finnish patients have one of two mutations—the so-called Fin major and Fin minor mutations.

Infants with CNSF are usually born prematurely and exhibit low birth weight and placentomegaly. CNSF manifests as heavy proteinuria, edema, and ascites, often in the first week of life and always by 3 months of age. Renal histology is nonspecific and

shows expansion of glomerular mesangium and dilations in the proximal and distal tubules. Untreated, these children suffer from malnutrition, poor growth, frequent infections, and thromboembolic complications. ESRD occurs invariably by mid-childhood. Corticosteroids do not ameliorate CNSF, but in mild forms, ACE inhibition, together with indomethacin, may be successful. The best therapeutic success has come from the approach of early dialysis, nephrectomy, and transplantation.

CNSF does not recur after transplantation. However, *de novo* nephrotic syndrome has been reported in about 25% of cases. It presents with proteinuria, hypoalbuminemia, and edema that may start immediately or as late as 3 years after transplantation. All the patients with post-transplantation nephrotic syndrome have been reported to have the homozygous Fin major genotype. Antibodies against fetal glomerular structures are found in most patients with post-transplantation nephrotic syndrome, and antibodies to nephrin are found in more than 50%. About half of patients with this nephrotic syndrome respond to steroids and cyclophosphamide, but in those who do not respond, the graft is usually lost. Plasma exchange to decrease antinephrin antibodies has been a useful adjunct. In the NAPRTCS database, vascular thrombosis and death with a functioning graft (mostly as a consequence of infectious complications) occur in 26% and 29% of cases, respectively, and account for a higher rate of graft failure in this particular group.

Mutations in the *NPHS2* gene located on chromosome 1 account for half of the congenital nephrotic syndrome cases in 80 European families and are autosomal recessive. Podocin is a podocyte-adapter protein required for proper targeting of nephrin into the slit diaphragm. Patients who are homozygous for podocin mutations develop early-onset steroid-resistant nephrotic syndrome, usually in infancy or early childhood, and usually progress to ESRD. Renal histology shows FSGS. Because podocin is a structural component of the glomerular filtration barrier, it was hypothesized that deficient podocin was the cause of renal disease and that recurrence would not occur. However, there are reports of recurrence in recipients from parents who are obligate carriers of

---

NPHS2 and in patients with heterozygous *NPHS2* mutations. The mechanisms remain unclear. Response to plasma exchange has been variable.

Mutations in *WT1* gene located on chromosome 11pl3 account for some cases of congenital nephrotic syndrome. *WT1* transcription factor plays a crucial role in the embryonic development of the kidney and genitalia. It is abundantly expressed in podocytes and controls cellular functions, such as nephrin expression. Patients with *WT1* mutations have moderate proteinuria, and renal biopsy reveals diffuse mesangial sclerosis (DMS) of glomeruli. *WT1* mutations can be found in isolated form, or as part of Denys-Drash syndrome. Denys-Drash syndrome is composed of progressive renal disease with nephrotic syndrome and DMS, Wilms tumor, and male pseudohermaphroditism. *WT1* mutations can also be associated with Frasier and WAGR syndromes. Frasier syndrome is composed of nephrotic syndrome with FSGS progressing to ESRD in

adolescence or young adulthood, normal female external genitalia, streak gonads, XY karyotype, and predisposition to gonadoblastoma. WAGR is composed of Wilms tumor, aniridia, urogenital abnormalities, and retardation. Patients with *WT1* mutations who have received kidney transplants have not been reported as developing nephrotic syndrome.

Membranous Nephropathy

Membranous nephropathy is uncommon in children, and post-transplantation recurrence is rarely seen. *De novo* membranous nephropathy occurs more frequently and affects up to 10% of transplanted children. It usually presents later than the recurrent disease, which usually becomes apparent within the first 2 post-transplantation years. The occurrence of *de novo* membranous nephropathy does not appear to affect graft outcome in the absence of rejection.

Systemic Lupus Erythematosus and the Vasculitides

In the pediatric transplant literature, recurrence of systemic lupus erythematosus (SLE) is rarely seen. Recurrence in adults is more common and may not manifest till several years after transplantation. In pediatric nephrology, it is most common to observe lupus nephritis progress to ESRD in adolescence. Because it is standard practice to defer transplantation until SLE has become clinically quiescent for at least 6 to 12 months, it is likely that the pediatric patient with SLE who receives a kidney transplant may not suffer from recurrence until young adult life.

Antineutrophil cytoplasmic antibody (ANCA)-positive glomerulonephritides can recur in the transplanted kidney. Wegener granulomatosis and pauciimmune glomerulonephritis recur in a small number of patients and can cause graft loss. Treatment with cyclophosphamide appears to be beneficial, and patients must be monitored carefully for signs of recurrence.

Metabolic Diseases

Primary Hyperoxaluria Type I

Oxalosis results from deficiency of hepatic peroxisomal alanine glyoxylate aminotransferase (AGT). Deficiency of this enzyme leads to deposition of oxalate in all body tissues, including the kidneys, myocardium, and bone. Renal transplantation alone does not correct the enzymatic deficiency, and graft loss is common because of oxalate mobilization from tissue deposits and subsequent deposition in the graft. Therapy with a combined liver and kidney transplantation has led to higher rates of success (see Chapter 12). The transplanted liver corrects the enzymatic deficiency and thus prevents further oxalate production. The well-functioning transplanted kidney excretes the mobilized plasma oxalate. Success of this approach is greatly facilitated by

immediate graft function with a good diuresis. If possible, combined liver and kidney transplantation

occurs early in the course of renal disease, preferably before the glomerular filtration rate (GFR) decreases below 20 to 25 mL per minute per 1.73 m^2. This serves to optimize outcome and prevent severe complications of the disease that may lead to irreversible morbidity.

Ideally, aggressive hemodialysis before transplantation is employed to decrease oxalate load to safe levels and minimize tissue oxalate deposition. The target plasma oxalate level is less than 50 mg/mL. At transplantation, a large donor kidney is used whenever possible to permit effective excretion of the oxalate burden. Early use of a calcineurin inhibitor may be deferred until the serum creatinine falls to the range of 1 to 2 mg/dL. Until this occurs, immunosuppression is accomplished with MMF, corticosteroids, and antibody induction. If early renal transplant dysfunction occurs, daily hemodialysis is continued. When good renal function is established, calcineurin-inhibitor therapy is begun. In addition, post-transplantation treatment includes pyridoxine, neutral phosphate, citrate, magnesium, and noncalciuric diuretics.

Nephropathic Cystinosis

Transplantation in children with cystinosis corrects the transport defect in the kidney, but not in other organs affected by the disease. Hypothyroidism, visual abnormalities, and central nervous system manifestations are not corrected by transplantation and require ongoing therapy with cysteamine and thyroid hormone. Cystine crystals can be found in the renal graft interstitium within macrophages of host origin. This does not result in recurrence of Fanconi syndrome or graft dysfunction.

Sickle Cell Anemia

The long-term graft survival rate for patients with sickle cell disease is lower, with only about 50% of grafts functioning beyond 3 years after transplantation. The improvement in the hematocrit results in higher numbers of abnormal red blood cells, leading to sickling episodes in the renal graft.

PRETRANSPLANTATION EVALUATION

The evaluation and preparation of a child for transplantation is essentially the same as for an adult (see Chapter 7). There are few absolute contraindications to kidney transplantation in children. Administration of immunosuppressive medications to immunocompromised children such as those who are HIV positive requires special consideration (see Chapter 11). Recent or metastatic malignancy precludes patients from transplantation. Patients with severe devastating neurologic dysfunction may not be suitable candidates; however, the wishes of the parents, as well as the potential for

long-term rehabilitation, must be considered.

Evaluation of the Potential Living Donor

As a general rule, it is possible to consider an adult donor of almost any size for a child, no matter how young (see Chapter 6). Living donation from siblings is usually restricted to donors older than 18 years, although the courts have given permission for younger children to donate under extraordinary circumstances.

Histocompatibility matching considerations are not different for pediatric recipients of kidneys from living donors than for adult recipients. HLA-identical transplants are optimal and enable the lowest amount of immunosuppression to be used, thereby minimizing steroid and other side effects. The first living donor for a child is usually a one-haplotype-matched parent. Siblings may become donors as they reach the age of consent. When considering transplantation from siblings, data suggest that kidneys from haploidentical donors with noninherited maternal HLA antigens function better in the long-term than do

---

those from donors with noninherited paternal HLA antigens (see Chapter 3). Second-degree relatives and zero-haplotype-matched siblings may also be considered as donors. The excellent results of nonbiologically related living donor transplants are not dependent on high degrees of HLA matching.

Evaluation of the Recipient

The evaluation of the potential pediatric transplant recipient is similar to that performed in adults, but because certain problems occur with more frequency in children, the emphasis may be different. It is important to establish the precise cause of ESRD in children whenever possible. Surgical correction may be required for certain structural abnormalities before transplantation. The precise cause of metabolic or glomerular disease should also be established if possible, because of the possibility of post-transplantation recurrence. Discussions of some common medical, surgical, and psychiatric issues in pediatric transplant candidates follow.

Neuropsychiatric Development

Infants. Infants with ESRD during the first year of life may suffer neurologic abnormalities. These include alterations in mental function, microcephaly, and involuntary motor phenomena, such as myoclonus, cerebellar ataxia, tremors, seizures, and hypotonia. The pathogenesis is unclear, although aluminum toxicity, prematurity, hypertensive crises, and dialysis-related seizures have been incriminated. Preemptive kidney transplantation or institution of dialysis at the earliest sign of head-circumference growth-rate reduction or developmental delay may ameliorate the problem. Some studies describe an improvement in psychomotor delay in some infants with successful transplantation, with a significant percentage of infants regaining

normal developmental milestones. Tests of global intelligence show increased rates of improvement after successful transplantation.

Older Children. It is often difficult to assess to what extent uremia contributes to cognitive delay and impairment in older children. Uremia has an adverse, but often reversible, effect on a child's mental functioning, and it may often cause psychological depression. It may be necessary to institute dialysis and improve the uremic symptoms before making a precise assessment of the child's mental function. Initiation of dialysis often clarifies the picture and permits progression to transplantation in situations in which it might otherwise have not seemed feasible. On the other hand, severely retarded children respond poorly to the constraints of ESRD care. A child with a very low IQ cannot comprehend the need for procedures that are often confusing and uncomfortable. In this situation, the family must be involved and supported in the decision to embark on a treatment course that does not include chronic dialysis or transplantation.

Seizures. Up to 10% of young pediatric transplant candidates have a seizure disorder requiring anticonvulsant treatment. Before transplantation, seizures should be controlled, whenever possible, with drugs that do not interfere with calcineurin inhibitor, sirolimus, or prednisone metabolism (see Chapter 5). Newer antiepileptic drugs such as levetiracetam (Keppra) are a good choice because they do not interfere with immunosuppression. Benzodiazepines can be used when circumstances permit. Carbamazepine does reduce calcineurin inhibitor and prednisone levels, but its effect is not as strong as that of phenytoin (Dilantin) or barbiturates. Should it prove necessary to use a drug that lowers immunosuppressive drug levels, a moderately augmented dose of prednisone may be given twice daily. The calcineurin inhibitor may need to be administered 3 times per day, or the dose adjusted upward, to achieve the desired trough levels, which should be monitored closely.

Psychoemotional Status

Psychiatric and emotional disorders are not, by themselves, contraindications to dialysis and transplantation; however, the involvement of health care professionals skilled in the care of affected children is mandatory. Primary psychiatric problems may be amenable to therapy and should not exclude children from consideration for transplantation. Experience with psychotropic drugs, such as selective serotonin reuptake inhibitors (SSRIs), has been very positive. As with antiseizure medications, it is important to recognize that certain drugs may interfere with the metabolism of some immunosuppressive medications. This has not been found to be a major issue with SSRIs such as citalopram, escitalopram, and sertraline (see Chapter 17).

Noncompliance is a particularly prevalent problem in adolescent transplant recipients. Patterns of medication and dialysis compliance should be established as part of the transplant evaluation. Psychiatric evaluation should be performed in high-risk cases. If

noncompliance is identified or anticipated, interventions should be in place before transplantation. These should include both social and psychiatric interventions, where possible. Psychosocial support systems must be identified and nurtured. Frequent medical and social work monitoring is crucial if the patient is to be rehabilitated both medically and psychosocially to the point at which the patient is a candidate for transplantation. The best outcomes will be achieved when there is close coordination between the medical and mental health providers. It is particularly important for the transplant and dialysis teams to stay in close communication as they prepare the patient for transplantation.

Cardiovascular Disease

Children and adolescents are unlikely to have overt cardiovascular disease that requires invasive diagnostic workup. Hypertension and chronic fluid overload during dialysis predisposes to left ventricular hypertrophy (LVH), hypertensive cardiomyopathy, and congestive heart failure. LVH may be present in up to 75% of pediatric transplant recipients, and peripheral resistance is often elevated. In children, as in adults, transplantation may be beneficial to cardiac function. Occasionally, the degree of pretransplantation cardiac compromise is so severe that heart transplantation must accompany kidney transplantation.

The importance of hypertension control in children with ESRD cannot be overemphasized. In the pretransplantation evaluation, blood pressure profiles and dialysis management must be carefully scrutinized. In the child who is hypertensive on dialysis, echocardiograms should be performed annually to assess ventricular hypertrophy and valve competence. In patients who require multiple antihypertensive drugs, bilateral nephrectomies may be required before transplantation.

Premature cardiovascular disease is a common feature of adults who have suffered childhood ESRD, and attention to adult cardiovascular disease risk factors in childhood may serve to minimize long-term morbidity and mortality. The coronary vessels of young adult dialysis patients have significant premature calcification (see Chapter 1). This may be the harbinger of atherosclerotic lesions. Control of calcium and phosphorus metabolism in the pretransplantation period is a potential way of ameliorating post-transplantation coronary heart disease. Statins may be indicated, and recommendations for their use in children have been made by the American Heart Association (see Sgambat et al).

Infection

Common Bacterial Pathogens. Urinary tract infections and infections related to peritoneal dialysis are the most common sources of bacterial infection in children with ESRD. Aggressive antibiotic therapy and prophylaxis of urinary tract

infections in children may effectively suppress infection, although pretransplantation

nephrectomy is occasionally required for recalcitrant infections in children with reflux. Peritonitis and related infections with peritoneal dialysis are discussed later (see “Children Receiving Peritoneal Dialysis”).

Cytomegalovirus. The incidence of CMV infection increases with age, and young children are unlikely to have developed CMV seropositivity. CMV IgM and IgG levels should be obtained with the pretransplantation evaluation, and these studies should be considered when planning post-transplantation CMV prophylaxis.

Epstein-Barr Virus. It is important to establish the Epstein-Barr virus (EBV) antibody status of the child. As with CMV, EBV infections and resultant seropositivity increase with age. Primary EBV infection, in the context of potent immunosuppression, may predispose to a particularly aggressive form of post-transplantation lymphoproliferative disorder (PTLD).

Immunization Status. Immunizations must be brought up to date whenever possible. Live viral vaccines are contraindicated in the immunosuppressed patient, and every effort must be made to complete these vaccinations before transplantation. This includes measles, mumps, rubella, and varicella vaccinations. Vaccination of the immunosuppressed host may fail to induce an adequate immune response, especially with the use of agents, such as MMF, that suppress antibody production.

Diphtheria and tetanus vaccine, as well as hepatitis B, can be given safely after transplantation, although pretransplantation administration is preferred. *Haemophilus influenzae-type* vaccine is also safe. Influenza and pneumococcal vaccines are recommended for the pediatric transplant recipient. Human papillomavirus vaccine is indicated in adolescent female recipients to prevent cervical cancer. Most of the available data on their effectiveness come from transplant recipients treated with cyclosporine or azathioprine. Studies are needed to address the immune responsiveness to vaccines under immunosuppression with newer agents.

Hemostasis

About 8% of graft loss in pediatric patients is caused by graft thrombosis. For this reason, it is particularly important to search for clues of a patient's tendency toward hypercoagulability, such as recurrent hemodialysis access clotting. In pediatric patients, a full coagulation workup includes prothrombin time, partial thromboplastin time, platelet count, protein S level, protein C level, factor V Leiden, antithrombin III level, G20210A prothrombin mutation, homocysteine level, MTHFR T677 mutation, antiphospholipid antibody, anticardiolipin antibody, β_2-glycoprotein 1 level, lipoprotein A level, and factor VIII level. If positive, perioperative and long-term anticoagulation can be used to minimize graft thrombosis.

Patients with Glomerulonephritis of Unknown Etiology

Pediatric patients are often referred for pretransplantation evaluation without having

had the diagnosis of ESRD established. As noted earlier, recurrence of glomerulonephritis or glomerulopathy is a significant concern in pediatric and adolescent recipients. For this reason, any patient with significant proteinuria or hypertension accompanying ESRD should have a serologic profile that can help classify the diagnosis of ESRD. This includes C3, C4, antinuclear antibody, anti-single-stranded and anti-double-stranded DNA, and ANCA titers.

Urologic Problems

Obstructive uropathy is the cause of ESRD in about 16% of transplanted children. Other causes of ESRD that are commonly associated with abnormalities of the urinary tract, such as reflux nephropathy, neurogenic bladder, prune belly syndrome, and renal dysplasia, account for another 20% of transplanted children. Because of this high frequency, urologic abnormalities should always be considered as a cause of ESRD of uncertain etiology in children and young adults. A history of voiding abnormalities, enuresis, nocturia, or recurrent urinary tract infections may be the only clue to an underlying urologic defect.

The presence of an abnormal lower urinary tract is not a contraindication to transplantation. Urologic problems are best addressed before transplantation. Malformations and voiding abnormalities (e.g., neurogenic bladder, bladder dyssynergia, remnant posterior urethral valves, urethral strictures) should be identified and repaired if possible. Children with urologic disease and renal dysplasia often require multiple operations to optimize urinary tract anatomy and function. Such procedures include ureteric reimplantation to correct vesicoureteric reflux; bladder augmentation or reconstruction; Mitrofanoff procedure (creation of a vesicocutaneous fistula using the appendix to provide for continent and cosmetically acceptable intermittent catheterization); and excision of duplicated systems or ectopic ureteroceles that may cause recurrent infections.

Bladder Augmentation. Urodynamic studies can provide important information about bladder capacity and function and help to define those situations that require bladder augmentation. Bladders that have high intravesical pressures are at risk for producing serious hydronephrosis in a transplanted kidney. Bladder augmentation is often required for patients with posterior urethral valve and some cases with small bladder capacity. Augmentation can be done using dilated ureter tissue, small intestine, or large intestine. Ureteric augmentation provides the best results because the ureteric mucosa is identical to the urinary bladder mucosa. Intestinal or colonic augmentation often requires frequent bladder irrigation and is often complicated by significant mucus secretion that can cause intermittent obstruction of the bladder stoma and lead to frequent urinary tract infections. Augmentation using gastric tissue causes severe dysuria because of the acidity of gastric secretions and has been abandoned in most centers. After bladder augmentation, most children require chronic intermittent

catheterization. Forceful hydrodilation as a substitute for bladder augmentation is used at some centers, but most physicians agree that it is very painful and futile, especially in children awaiting deceased donor transplantation.

If a child has a neurogenic bladder, a bladder augmentation, or other voiding abnormality, it is usually possible to teach a parent or the patient clean, intermittent self-catheterization. This can be done in transplant recipients safely and successfully. However, urinary tract infection may occur when catheterization technique is poor. In addition, noncompliance with self-catheterization may lead to partial obstruction and subsequent graft dysfunction.

In some studies, graft outcome in children with urologic problems is inferior to that of children with normal lower urinary tracts. In addition, in recipients with an abnormal bladder, there is an increased incidence of post-transplantation urologic complications and urinary tract infection. Nevertheless, in centers with skilled pediatric urologists, children with ESRD as a consequence of urologic malformations can be successfully transplanted.

Renal Osteodystrophy

Aggressive diagnosis and treatment of hyperparathyroidism, osteomalacia, and adynamic bone disease are important in the pretransplantation period. Control of hyperparathyroidism with vitamin D analogues, or even parathyroidectomy, may be required. Failure to do so may predispose to post-transplantation hypercalcemia and limit the growth potential of a successful transplant recipient.

Children Receiving Peritoneal Dialysis

It has been generally accepted that children being treated with peritoneal dialysis have graft and patient survival rates that are similar to those of children receiving hemodialysis, although they may have higher risk for graft thrombosis, as may those children who receive preemptive transplants. The etiology of this observation is not clear. Therefore, a full coagulation workup should be considered before transplantation. Peritoneal dialysis may, in fact, facilitate transplant surgery, especially in very young and small infants. Repeated peritoneal fluid cycling expands the abdomen and creates adequate space for extraperitoneal placement of the relatively large adult kidney. Extraperitoneal placement of the graft is desirable because it may allow for continued peritoneal dialysis after transplantation in the event of DGF, and patients can tolerate oral feeds and medications sooner because of minimal bowel manipulation. However, intraperitoneal graft placement is not an absolute contraindication to post-transplantation peritoneal dialysis, should it become necessary.

A recent episode of peritonitis or exit-site infection in a child awaiting a transplant

does not necessarily preclude transplantation. Potential transplant recipients should be appropriately treated for 10 to 14 days and have a negative peritoneal fluid culture off antibiotic treatment before contemplating transplantation. In addition, the preoperative peritoneal cell count should not suggest peritonitis. If a chronic exit-site infection is present at the time of surgery, the catheter should be removed and appropriate parenteral antibiotics administered. An overt tunnel infection should be treated before transplantation. The incidence of post-transplantation peritoneal dialysis-related infections is low. However, peritonitis and exit-site infection should be considered in the differential diagnosis in any child with unexplained fever after transplantation, and early sampling of the peritoneal fluid should be pursued. Such infections typically respond to appropriate antibiotic therapy, although catheter removal may be necessary for recurrent infections. In the absence of infections, the peritoneal catheter may be left in place until good graft function has been established for 2 to 3 weeks.

Nephrotic Syndrome

In children with glomerular diseases, proteinuria usually diminishes as kidney function deteriorates and ESRD ensues. Occasionally, florid nephrotic syndrome may persist, particularly in children with FSGS. Persistence of heavy proteinuria causes a hypercoagulable state and increases the risk for graft thrombosis and thromboembolic complications at the time of surgery, making fluid management difficult because of leakage of fluids into the extravascular space, which may lead to delayed graft function and adversely affect graft outcome. Control of heavy proteinuria before transplantation is important and can sometimes be achieved with prostaglandin inhibitors, although renal embolization or bilateral laparoscopic nephrectomy may be required.

In the child with CNSF, unilateral or bilateral nephrectomy is usually performed early in the course of the disease to allow for better skeletal growth while on dialysis and to prevent infectious and thromboembolic complications. Nephrotic syndrome associated with isolated *WT1* mutations or in association with Denys-Drash, Frasier, or WAGR syndromes usually requires early bilateral nephrectomy as part of the treatment of Wilms tumor.

Pretransplantation Nephrectomy

Nephrectomy should be avoided if possible because leaving the kidneys *in situ* may facilitate fluid management during dialysis, an important consideration for small children in whom fluid balance may be tenuous. Nephrectomy may be indicated for severely hypertensive patients in whom blood pressure control is suboptimal despite optimal fluid removal and use of a multiple antihypertensive agents. Intractable urinary tract infection, in the presence of hydronephrosis or severe reflux, may also

require nephrectomy before transplantation. Occasionally, nephrectomy is required to create adequate space for placement of the adult graft in a small infant. This is frequently the case in autosomal recessive polycystic kidney disease, in which the enlarged kidneys occupy the abdominal cavity, and may impair diaphragmatic movement, causing respiratory difficulty.

Portal Hypertension

Portal hypertension may occur in certain forms of ESRD common in children, such as congenital hepatic fibrosis, which may accompany autosomal recessive polycystic kidney disease, and nephronophthisis. The manifestations of congenital hepatic fibrosis must be controlled; esophageal varices require sclerotherapy or portosystemic shunting. If neutropenia and thrombocytopenia are present as a result of hypersplenism, partial splenectomy or splenic embolization may occasionally be required.

Prior Malignancy

Wilms tumor is the most common renal malignancy in children and the principal malignancy producing ESRD in children. Post-transplantation recurrence of Wilms tumor has been described in up to 6% of patients. Patients with recurrent Wilms tumor tend to be younger and have a shorter interval from tumor recognition to transplantation. A disease-free period of 2 years from the time of remission should be observed before transplantation. Premature transplantation has been associated with overwhelming sepsis, which may be related to recent chemotherapy. The presence of a primary nonrenal malignancy is not an absolute contraindication to transplantation, although an appropriate waiting time must be observed between tumor extirpation and transplantation (see Chapter 7).

Preemptive Transplantation

Nearly 25% of all pediatric transplantations are now performed without the prior institution of dialysis. The percentage is even higher for recipients of living donors and is much higher than that reported in adults. The incidence of preemptive transplantation is nearly double in white children (30%) compared with African American (14%) and Hispanic (16%) children. In children and in adults, there is a significant improvement in graft survival for patients who have not received pretransplantation dialysis.

Nutrition

Poor feeding is a prominent feature of uremia in children. Aggressive nutritional support is essential. Early gastrostomy or nasogastric tube feeding is often employed to improve caloric intake and promote growth, especially in children started on dialysis

therapy at a young age. Because of technical difficulty and a resultant possibility of graft loss, a weight of 8 to 10 kg is used as a target weight for transplantation at most centers. This weight may not be reached until 2 years of age, even with the most aggressive nutritional regimens. Transplantation in children weighing less than 5 to 8 kg has been successfully performed at some centers.

PERIOPERATIVE MANAGEMENT OF THE PEDIATRIC RENAL TRANSPLANT RECIPIENT

Preparation for Transplantation

For living donor transplants, some programs commence immunosuppression in the week before the transplant date. A final crossmatch is performed within 1 week of transplantation, and the patient is evaluated clinically to ensure medical stability. Laboratory tests obtained at admission permit detection of metabolic abnormalities that require correction by dialysis. Aggressive fluid removal is discouraged in the immediate preoperative period to reduce the risk for delayed graft function (see Chapter 9). Preoperative immunosuppression is discussed later.

Intraoperative Management

Methylprednisolone sodium succinate (Solu-Medrol), 10 mg/kg, is given intravenously at the beginning of the operation. Close attention is paid to blood pressure and hydration status in an attempt to reduce the incidence of DGF. Typically, a central venous catheter is inserted to monitor the central venous pressure (CVP) throughout the operation. To achieve adequate renal perfusion, a CVP of 12 to 15 cm H_2O should be achieved before removal of the vascular clamps; a higher CVP may be desirable in the case of a small infant receiving an adult-sized kidney. Dopamine is usually started in the operating room at 2 to 3 μg/kg per minute and increased as required and is continued for 24 to 48 hours postoperatively. It is used to facilitate diuresis and perhaps to effect renal vasodilation. The mean arterial blood pressure is kept above 65 to 70 mm Hg by adequate hydration with a crystalloid solution or 5% albumin and, if necessary, the use of dopamine at higher doses. Blood transfusion with packed red blood cells may be required in very small recipients because the hemoglobin may drop as a result of sequestration of about 150 to 250 mL of blood in the transplanted kidney. Mannitol and furosemide may be given before removal of the vascular clamps to facilitate diuresis. Urine volume is replaced immediately with 0.45% or 0.9% normal saline. Occasionally, an intra-arterial vasodilator, such as verapamil, is used to overcome vasospasm that may impair renal perfusion.

Postoperative Management

Because of the small size of young children, fluid management must be fastidious. Urine output should be replaced on a milliliter-for-milliliter basis with 0.45% or 0.9% normal saline continued for 24 to 48 hours. Insensible water losses are replaced with a dextrose-containing crystalloid. Potassium replacement may be required. Dextrose is not added to the replacement solution and is only used as part of the insensible water loss replacement solution. Withholding dextrose in the urine replacement solutions helps to prevent post-transplantation hyperglycemia and osmotic diuresis. The lack of concentrating ability of the newly transplanted kidney accounts for an obligatory high urine output that may be observed in the first few post-transplantation days. As the kidney function improves and the serum creatinine levels fall close to normal values, urinary concentrating ability recovers, and urine output decreases from several liters per day to amounts that begin to match daily fluid intake. At this time, urine output replacement can be stopped, and daily fluid intake is usually set to provide about 150% to 200% of the normal daily maintenance needs, preferably administered orally.

Hypertension is commonly observed. Pain is an important cause of hypertension in the immediate postoperative period, and adequate analgesia may be all that is required to control blood pressure. Hypertension is rarely aggressively

corrected in the immediate postoperative period to avoid sudden swings in blood pressure that may impair renal perfusion. Electrolyte disorders encountered early in the postoperative course are discussed elsewhere. Prophylaxis against CMV infection is outlined in Tables 16.3 and 16.4 and in Chapter 11.

TABLE 16.3 Cytomegalovirus (CMV) prophylaxis protocol at the Mattel Children's Hospital at UCLA pediatric renal transplant program

Donor CMV status	Recipient CMV status	Ganciclovir[a]
Positive	Positive	Yes
Positive	Negative	Yes
Negative	Positive	Yes

Negative	Negative	No

[a] Ganciclovir is valganciclovir ijiven intravenously initially (2.5 mg/kg dai dosing per Table 16.4.

PEDIATRIC IMMUNOSUPPRESSIVE PROTOCOLS

Readers are referred to Chapter 5 for a full discussion of transplantation immunosuppressive agents and protocols and to Tables 16.5, 16.6, and 16.7. The construction of the immunosuppressive protocol for pediatric transplantation is similar to that for adults. Because of the long-term toxicities of corticosteroids, many pediatric renal transplantation centers have moved toward steroid avoidance, and as of 2005, about 70% of children receive steroids. Table 16.5 represents one version of a steroid avoidance protocol that includes extended daclizumab (Zenapax), tacrolimus, MMF, and frequent protocol biopsies. Rejection rates with this protocol are low, and growth and renal function are significantly improved. However, there have been a few reports of increased incidence of rejection when MMF is held or decreased because of side effects. Unlike steroid-based regimens, it remains unclear whether MMF can be safely held without steroids. A steroid-free regimen using Thymoglobulin induction followed by maintenance therapy with cyclosporine and MMF has also been successful. Induction therapy with a biologic agent is employed in about 70% of transplant recipients. Thymoglobulin can be used to provide adequate initial immunosuppression and allow delayed introduction of the calcineurin inhibitor in cases of DGF, or to provide intensified immunosuppression in the highly sensitized transplant recipient. When transplantation is contemplated in a child with prior malignancy, a two-drug regimen, or even monotherapy, may be considered to minimize the effect immunosuppressive drugs may have on immune surveillance. In this situation, the use of antibody induction is generally avoided, and living donation is encouraged to provide the best HLA match.

TABLE 16.4 Valganciclovir (Valcyte) Dosing

Creatinine Clearance (mL/min/1.73m^2), Schwartz Formula	Patient Weight <30 kg	Patient Weight 30-50 kg	Patient Weight ≥50 kg
≥60	10-12 mg/kg PO daily	450 mg PO daily	900 mg PO daily
40-59	5-6 mg/kg PO daily	225 mg PO daily	450 mg PO daily
25-39	5-6 mg/kg PO every other day	225 mg PO every other day	450 mg PO every other day
10-24	5-6 mg/kg PO twice weekly	225 mg PO twice weekly	450 mg PO twice weekly

TABLE 16.5 Steroid Avoidance Immunosuppressive Protocol for Pediatric Kidney Transplantation at the Mattel Children's Hospital at UCLA

Pretransplantation (1 Week in Living Donor Recipients Only)

- MMF: 600 mg/m^2/dose twice daily

- + Famotidine: 1 mg/kg/dose twice daily (maximum, 20 mg twice daily; other H_2 blockers, except cimetidine, or H^+ pump blockers may be used)

Pretransplantation (6 to 24 Hours)

- Daclizumab: 2 mg/kg in 50 mL of normal saline IV over 30 min
- MMF: 600 mg/m^2 PO/IV within 6 hr

Intraoperatively

- Solu-Medrol: 10 mg/kg IV at the beginning of surgery (maximum dose of 1 g)

Immediate Postoperative Period

- MMF: 600 mg/m^2/dose IV q 12 hr*
- Cyclosporine: 10-15 mg/kg/day PO divided twice daily. For children who weigh less than 10 kg or are younger than 6 yr of age, give 400-500 mg/m^2/day divided 3 times daily.† The dose is adjusted to achieve trough levels of 250-350 ng/mL and/or C2 levels of 1200-1500 ng/mL.

- *Or:*
- Tacrolimus: 0.15-0.2 mg/kg/day PO divided twice daily to achieve levels of 8-12 ng/mL†
- + Famotidine or H_2 blocker

Maintenance Therapy

- Daclizumab: 1 mg/kg at 2, 4, 6, 8, 11 wk, 4 mo, 5 mo, 6 mo after transplantation
- MMF: 600 mg/m^2/dose PO twice da ily until cyclosporine/tacrolimus levels area adequate; then can switch to 300-450 mg/m^2/dose PO twice daily‡
- Cyclosporine/tacrolimus: dose adjusted to achieve the desired trough levels (see Chapter 5, Table 5.8).

* The drug is given orally when the patient tolerates oral intake.

† Cyclosporine/tacrolimus is started once urine output has been established and the serum creatinine level is below 2 mg/dL or less than 50% of its baseline value before transplantation.

‡ The dose can be spread to a 3 times daily schedule if gastrointestinal symptoms develop early. H_2, histamine-2; MMF, mycophenolate mofetil.

Corticosteroids

Corticosteroids have decreased in use in many pediatric immunosuppressive protocols because of their toxicity. Steroid avoidance protocols have been successful and safe in children.

In children, retarded skeletal growth is the most important side effect. Concerns remain about familiar side effects, such as hypertension, obesity, diabetes mellitus, hyperlipidemia, osteopenia, and aseptic necrosis. Cosmetic side effects, such as cushingoid facies and acne, may tempt children and adolescents to stop taking their immunosuppressive drugs. Steroids are employed in children in certain circumstances including retransplantation, high panel reactive antibodies (PRAs), recurrent disease, and preexisting use (Table 16.6). However, children are quickly tapered to lower doses and when possible converted to alternate-day steroids.

TABLE 16.6 Steroid-Based Immunosuppressive Protocol for Pediatric Kidney Transplantation at the Mattel Children's Hospital at UCLA

Pretransplantation (1 Week in Living Donor Recipients Only)

- Prednisone: 0.5 mg/kg daily (minimum = 20 mg/day)
- MMF: 600 mg/m^2/dose twice daily
- + Famotidine: 1 mg/kg/dose twice daily (maximum = 20 mg twice daily; other H_2 blockers, except cimetidine, or H^+ pump blockers may be used)

Pretransplantation (6 to 24 Hours)

- Daclizumab: 1 mg/kg in 50 mL of normal saline IV over 30 min
- MMF: 600 mg/m^2 PO/IV within 6 hr

Intraoperatively

- Solu-Medrol: 10 mg/kg IV at the beginning of surgery (maximum dose: 1 g)

Immediate Postoperative Period

- Solu-Medrol: 0.5 mg/kg/day IV (minimum dose = 20 mg/day)*
- MMF: 600 mg/m^2/dose IV every 12 hr*
- Cyclosporine: 10-15 mg/kg/d PO divided twice daily. For children who weigh less than 10 kg or are younger than 6 yr of age, give 400-500 mg/m^2/day divided 3 times daily.† The dose is adjusted to achieve trough levels of 250-350 ng/mL and/or C2 levels of 1200-1500 ng/mL.
- *Or:*
- Tacrolimus: 0.15-0.2 mg/kg/day PO divided twice daily to achieve levels of

8-12 ng/mL[†]

- + Famotidine or H_2 blocker

Maintenance Therapy

- Daclizumab: 1 mg/kg at 2, 4, 6, and 8 wk after transplantation
- Prednisone: dose tapering started 1 wk after transplantation and continued to reach a maintenance dose 0.07-0.1 mg/kg/d by 2-3 months
- MMF: 600 mg/m^2/dose PO twice daily with cyclosporine; 300-450 mg/m^2/dose PO twice daily with tacrolimus[‡]
- Cyclosporine/tacrolimus: dose adjusted to achieve the desired trough levels (see Chapter 5, Table 5.8)

[*] The drug is given orally when the patient tolerates oral intake.

[†] Cyclosporine/tacrolimus is started once urine output has been established and the serum creatinine level is below 2 mg/dL or less than 50% of its baseline value before transplantation.

[‡] The dose can be spread to a 3 times daily schedule if gastrointestinal symptoms develop early.

H_2, histamine-2; MMF, mycophenolate mofetil.

Calcineurin Inhibitors

There are some important differences in the use of cyclosporine and tacrolimus between adults and children. Children, particularly those younger than 2 years, may require higher doses than adults when calculated on a milligram per kilogram of body weight basis. The higher dose requirement is believed to be the result of a higher rate of metabolism by the hepatic cytochrome P-450, resulting in faster clearance. Dosing based on surface area, or thrice-daily dosing, appears to provide better therapeutic levels in smaller children and in children in whom metabolism is accelerated (e.g., patients receiving certain anticonvulsant medications). The use of peak-level monitoring of cyclosporine (C2 levels, see Chapter 5) that has been recommended for adults has not been independently validated in children. The recommended drug levels of cyclosporine and tacrolimus for children are similar to those recommended for adults (see

Chapter 5). Studies comparing the efficacy of cyclosporine and tacrolimus in children have tended to favor tacrolimus in terms of the incidences of both acute rejection and graft loss. In the NAPRTCS database, however, there was little difference between the two drugs when used in combination with MMF. Concern generated from data collected in the late 1980s regarding a much higher incidence of PTLD in children receiving tacrolimus has largely mitigated.

TABLE 16.7 Guidelines for Drug Dose Tapering in Pediatric Renal Transplant Recipients

1. Cyclosporine/Tacrolimus

Minimal or no change is made in the first 4 weeks to allow for faster tapering of prednisone.

Dose reduction should not exceed 10% to 20%.

Cyclosporine/tacrolimus and prednisone doses should not be lowered on the same day (risk for precipitating an acute rejection).

Serum creatinine and cyclosporine/tacrolimus levels should be checked 2 to 3 days after each change and before the next change is made.

(The same guidelines are applied to patients treated with tacrolimus.)

2. Prednisone

Start tapering the dose 2 to 3 weeks after transplantation if stable and cyclosporine/tacrolimus level is within the desired range.

Initial dose tapering is by 2.5 mg each time, about 10% (may reduce by 5 mg if total dose is >2 mg/kg). Once a 10-mg dose is reached, dose reduction is by 1 mg each time.

Longer periods of time should elapse before further tapering at the lower dose range.

Cyclosporine/tacrolimus and prednisone doses should not be lowered on the same day.

Serum creatinine and cyclosporine/tacrolimus levels should be checked 2 to

3 days after each change and before the next change is made.

3. **Mycophenolate Mofetil**

Dose reduction is only indicated if hematologic or gastrointestinal side effects develop.

Dose reduction is done in 30% to 50% increments.

It can be safely withheld for a few days or up to 3 to 4 weeks for severe side effects with steroid-based regimens.

The side-effect profile of the calcineurin inhibitors in children is similar to that seen in adults (see Chapter 5). Hirsutism, gingival hyperplasia, and coarsening facial features may be troublesome in children receiving cyclosporine, particularly Hispanic and African American children. In the adolescent population, especially girls, these side effects may be devastating, causing severe emotional distress and possibly leading to dangerous noncompliance. Switching to tacrolimus may be helpful, although hair loss may follow. Seizures are observed more commonly in children treated with calcineurin inhibitors than in adults. Neurologic symptoms tend to be more severe with tacrolimus. Children, like adults, are more likely to develop hypercholesterolemia and hypertriglyceridemia with cyclosporine and may be candidates for lipid-lowering agents. Glucose intolerance is less common than in adults and occurs in less than 5% of children; it is more common with tacrolimus. Overt diabetes mellitus may occasionally occur. There has been a steady trend toward using tacrolimus rather than cyclosporine for children, and as of 2007, about 70% of pediatric recipients were receiving tacrolimus-based therapy.

Mycophenolate Mofetil and Sodium Mycophenolate

MMF is used in about two thirds of U.S. pediatric renal transplant recipients and has largely replaced azathioprine. The capacity of MMF to reduce the incidence of acute

rejection episodes relative to azathioprine is similar in children to that described in adults (see Chapter 5). In children, as in adults, gastrointestinal and hematologic side effects can be troublesome and may respond to dose reduction. Conversion to enteric-coated mycophenolate sodium (Myfortic) gives equivalent dosing as MMF and has been claimed to reduce gastrointestinal side effects. Therapeutic drug monitoring of MMF has been proposed for children but has not achieved widespread use. MMF has been used successfully in children for the treatment of steroid-resistant acute rejection.

Sirolimus

Sirolimus currently is used in most centers as a second-line agent. Reported efficacy and side-effect profiles mimic the adult experience. Concerns have been raised that sirolimus in adults results in decrease testosterone level, spermatogenesis disruption, and deleterious effects on the testis. The impact of this gonadal impairment has not been studied in pediatric recipients, and monitoring of luteinizing hormone, follicle-stimulating hormone, and testosterone levels may be prudent. An NAPRTCS-sponsored clinical trial to evaluate the use of sirolimus for a primary agent in combination with low-dose tacrolimus in *de novo* pediatric renal transplant recipients has shown an unacceptably high level of PTLD. Additionally, *de novo* calcineurin inhibitor avoidance with sirolimus and CellCept has resulted in an up to 30% incidence of biopsy-proven acute rejection. Conversion to sirolimus 3 to 6 months after transplantation to prevent chronic allograft nephropathy is under investigation. Metabolism of sirolimus may be more rapid in children than in adults, and more frequent dosing may be advisable.

Biologic Immunosuppressive Agents

The indications for the use of antibody-induction are discussed in Chapter 5 and do not differ between adults and children. More than 70% of children are treated with antibody induction, most frequently with nondepleting agents. The side-effect profiles of these agents are also similar. In pediatric living donor transplantation, there is close to a 10% advantage in the 5-year graft survival rate when antibody induction is used. Acute rejection episodes are about 25% less frequent and tend to occur later.

The non-lymphocyte-depleting anti-CD25 monoclonal antibodies are daclizumab (Zenapax) and basiliximab (Simulect). They may be of particular benefit in children because of their effectiveness, ease of administration, and absence of side effects. In an open-label multicenter pediatric study with daclizumab used in addition to a triple-drug regimen with either cyclosporine or tacrolimus together with MMF and prednisone, the rate of acute rejection was found to be only 7% at 6 months and 16% 1 year after transplantation. All rejections were mild and steroid responsive. No first-dose or cytokine-release effect or anaphylactic reactions were observed. Rates of opportunistic infections were not increased.

The polyclonal antilymphocyte preparation in most common use for induction in pediatrics is rabbit antithymocyte globulin (Thymoglobulin). Thymoglobulin suppresses

CD3-, CD4-, and CD8-bearing T cells in pediatric patients and has anti-B-cell effects. The lymphocyte-depleting effects of thymoglobulin used

as induction therapy may last many months without increasing the risk for viral infection. Thymoglobulin has also been used in episodes of DGF and for steroid avoidance or steroid withdrawal protocols.

ACUTE REJECTION IN PEDIATRIC TRANSPLANTATION

Acute rejection episodes in pediatric renal transplantation account for about 10% of graft failures. With standard immunosuppressive therapy, an acute rejection episode is experienced in about 14% of recipients of living donor transplants and 18% of deceased donor transplant recipients. The first rejection episode occurs within the first 3 months after transplantation in about half of patients, with higher frequency and earlier recurrence in recipients of deceased donor transplants. African American race, delayed graft function, no antibody induction, and poor HLA matching may predispose to rejection episodes. In children, as in adults, acute rejection is the single most important predictor of chronic rejection. It precedes graft failure from chronic rejection in more than 90% of cases. Chronic allograft failure is the most common cause of graft loss in children.

Diagnosis of acute rejection in the very young transplant recipient is not always straightforward and requires a high index of suspicion. Because most small children are transplanted with adult-sized kidneys, the elevation in serum creatinine may be a late sign of rejection as a result of the large renal reserve compared with the body mass. Significant allograft dysfunction may be present with little or no increase in the serum creatinine level. One of the earliest and most sensitive signs of rejection is the development of hypertension along with low-grade fever. In children, any increase in serum creatinine, especially if accompanied by hypertension, should be considered a result of acute rejection until proved otherwise. Late diagnosis and treatment of rejection are associated with higher incidence of resistant rejections and graft loss.

The differential diagnosis of acute allograft dysfunction in children is similar to that in adults (see Chapter 9). Renal biopsy is the gold standard for diagnosis. The procedure has been shown to be safe in pediatric patients, with a low complication rate. We recommend the administration of DDAVP (0.3 μg/kg given intravenously) 1 hour before the procedure in any child with allograft dysfunction to correct any potential bleeding tendency. Urinalysis and culture, viral cultures, and ultrasound and radionuclide imaging studies are used to diagnose other causes of graft dysfunction (see Chapters 10 and 13).

Treatment of Acute Rejection

The techniques used to treat acute rejection are similar in children to those used in adults (see Chapter 5). Complete reversal of acute rejection, as judged by a return of

the serum creatinine level to baseline, is achieved in about half of children; 40% to 45% achieve partial reversal, and graft loss occurs in the remainder. Complete reversal from acute rejection is even less likely with subsequent rejection episodes. Younger transplant recipients are at higher risk for graft loss from acute rejection.

Corticosteroids

In children, as in adults, high-dose corticosteroid pulses are the first line of treatment of acute rejection, and about 75% of episodes are responsive to treatment. After the diagnosis is made, intravenous methylprednisolone is given in doses that range from 5 to 10 mg/kg per day for 3 to 5 days. After completing therapy, the maintenance corticosteroid is resumed at the prerejection level, or is increased and then tapered to baseline levels over a few days. For those on a steroid avoidance protocol, conversion to low-dose maintenance steroids should

---

be considered. The serum creatinine level may rise slightly during therapy and may not go back to baseline until 3 to 5 days after therapy is completed.

Lymphocyte-Depleting Agents

Both OKT3 and Thymoglobulin reverse up to 90% of the acute rejection episodes that do not respond to steroids. In most pediatric centers, Thymoglobulin has replaced OKT3 because of its lower side-effect profile. The standard dose of Thymoglobulin for acute rejection is 1.5 mg/kg/day for 7 to 14 days or can be dosed based on T-cell subsets. Administration through a peripheral vein often leads to vein thrombosis or thrombophlebitis. Therefore, peripherally inserted central catheter line placement is recommended before administration. To avoid allergic reactions, the patient should receive intravenous premedication consisting of methylprednisolone and diphenhydramine hydrochloride (Benadryl) 30 minutes before infusion. Weight-appropriate acetaminophen dosing should be given before and 4 hours after commencement of infusion for fever control. Vital signs should be monitored every 15 minutes during the first hour of infusion and then hourly until infusion is complete.

Side effects of Thymoglobulin in children are similar to those described in adults and include leukopenia and thrombocytopenia, which should be monitored with daily blood counts. The dose should be reduced by 50% for a platelet count of 50,000 to 100,000 cells/mL or a white blood cell count of less than 3000 cells/mL. Administration should be stopped if counts fall lower. Azathioprine, MMF, and sirolimus should be held during the course of treatment because they exacerbate hematologic side effects.

Refractory Rejection

Refractory rejection usually refers to episodes of acute rejection that do not respond to, or reoccur after, treatment with high-dose corticosteroids and lymphocyte-depleting agents. About 75% of cases can be reversed by switching to tacrolimus or

adding MMF, if this drug had not been part of the immunosuppressive protocol. Relatively high doses and trough levels are required. Sirolimus is a potential treatment option, although experience is limited. If a renal biopsy shows that the refractory rejection has a component of antibody-mediated rejection (as manifested by positive staining for C4d), therapy with high-dose intravenous immune globulin, Rituximab, and plasma exchange can be successfully used. Whenever such aggressive immunosuppressive therapy is employed, the risk for opportunistic infections and post-transplantation lymphoma increases. Viral prophylaxis and infection surveillance are critical.

NONCOMPLIANCE IN PEDIATRIC TRANSPLANTATION

At least half of pediatric deceased donor transplant recipients demonstrate significant noncompliance. In adolescents, this figure exceeds 60%. Noncompliance is the principal cause of graft loss in up to 15% of all pediatric kidney transplant recipients; for retransplanted patients, this figure may exceed 25%. Reversible and irreversible episodes of graft dysfunction related to noncompliance occur in up to 40% of adolescents and are somewhat less frequent in younger children. Patterns of noncompliance vary from partial compliance to complete noncompliance. Partial compliance ranges from the occasional missed dose to an occasional extra dose. It is most commonly the result of forgetfulness, misunderstanding of a dose change or modification, or the presence of events that lead to the belief that medications are not helping. In children, complete noncompliance is often the result of underlying emotional or psychosocial stress.

Measuring Compliance

Methods to measure compliance are crude and provide only a general estimate at best. The easiest method is asking patients directly about their compliance; patients, however, tend to tell physicians what they want to hear. Assessments made by patients of failure to take medications are often accurate, whereas denials of noncompliance are not. Serum drug-level monitoring is only helpful when the drug level is either inexplicably low or high. Other methods to measure noncompliance include pill counts and assessment of prescription refill rates. A continuous microelectronic device, usually attached to the cap of the medication bottle, records each opening of the bottle as a presumptive dose and records the time and frequency of taking the medication. Recorded data can then be retrieved and an assessment of compliance made.

Predicting Compliance

Pretransplantation prediction of post-transplantation noncompliance is difficult. Risk factors include a disorganized family structure, female sex, adolescence, and a history of previous graft loss as a consequence of noncompliance. Personality problems related

to low self-esteem and poor social adjustment are found with higher frequency in noncompliant patients. Studies indicate that compliance has no correlation with intelligence, memory, education, or the number of drugs that a patient takes, although the daily frequency of taking medications may affect compliance greatly. A linear decline in compliance rates has been demonstrated with increasing number of doses per day. Frequent clinic visits may improve compliance. Noncompliance in children must be suspected when there is unexplained diminution in cushingoid features, sudden weight loss, or unexplained swings in graft function or trough blood levels of the calcineurin inhibitors.

Strategies to Improve Compliance

Education, planning dose regimens, clinic scheduling, communication, and getting patients involved in the medical management are the main strategies. The child should know that the physician is their advocate and is interested in how they take their medications. Providing patients with specific reminders or cues to which the medication can be tied can be of great help. These cues should be simple and preferably part of the patient's daily activities, such as meal times, daily rituals, specific clock times, a certain television program, tooth brushing, shaving, and so forth. Contracting with pediatric patients and rewarding them is another strategy to enhance compliance. Finally, asking the same questions about compliance each visit and explaining the consequences of noncompliance repeatedly reinforce the compliance message and physician interest.

Psychological Intervention

Behavior modification programs and other means of psychological intervention may be beneficial in some patients. In the pretransplantation period, an ongoing program of counseling should be undertaken in high-risk patients. Clearly defined therapeutic goals should be set while the patient is receiving dialysis, and family problems that are recognized in the pretransplantation period should be addressed before activation on the transplant list. The presence of at least one highly motivated caretaker is a helpful factor in long-term graft success.

Adolescence brings with it rapid behavioral and bodily changes. The adolescent's strong desire to be normal conflicts with the continued reminder of chronic disease that the taking of medication engenders; this tendency is particularly true when medications are taken many times a day and alter the

---

physical appearance. Ambivalence between the desire for parental protection and autonomy, combined with a magical belief in his or her invulnerability, sets the stage for experimentation with noncompliance. Adolescents with psychological or developmental problems may use impulsive noncompliance during self-destructive episodes. The transplantation teams must be aware of these developmental issues so

that they can initiate appropriate psychological intervention before the onset of significant noncompliant behavior.

GROWTH

Retarded skeletal growth is a constant feature in children with chronic renal failure and ESRD. The severity of growth retardation is directly related to the age of onset of renal failure; the earlier the onset, the more severe. Renal osteodystrophy, metabolic acidosis, electrolyte disturbances, anemia, protein and calorie malnutrition, delayed sexual maturation, and accumulation of uremic toxins have all been implicated in the development of growth retardation.

Growth retardation is typically assessed by the *standard deviation score* (SDS) or height deficit score (also known as the *Z score)*. These measure the patient's height compared with that of unaffected children of similar age.

Determinants of Post-transplantation Growth

Growth improves after transplantation; however, full catch-up growth is not realized in most patients. The following factors have a major influence on post-transplantation growth.

Age

Children younger than 6 years of age have the lowest standard deviation scores before transplantation, and these exhibit the best improvement in their SDS after transplantation. Two years after transplantation, infants younger than 1 year of age have an improvement in their SDS by 1 full standard deviation (SD), compared with an improvement of only 0.5 SD for those between 2 and 5 years of age, and 0.1 SD in those between the ages of 6 and 12 years. Children older than 12 years of age tend to have minimal or no growth after transplantation. Older children occasionally continue to grow into puberty; however, the growth spurt experienced by most growing children at this age may be blunted or lost.

The fact that youngest children benefit the most in statural growth from early transplantation provides a strong argument for expedited transplantation in an attempt to optimize and perhaps normalize stature. In addition, earlier transplantation allows less time for growth failure while receiving dialysis and therefore a lesser requirement for catch-up growth.

Corticosteroid Dose

The precise mechanism by which steroids impair skeletal growth is unknown. They may reduce the release of growth hormone, reduce insulin-like growth factor (IGF) activity, directly impair growth cartilage, decrease calcium absorption, or increase renal phosphate wasting. Strategies to improve growth include the use of lower daily doses of

steroids, the use of alternate-day dosing, dose tapering to withdrawal, or complete avoidance. Conversion to alternate-day dosing should be considered in selected, stable patients in whom compliance can be ensured.

Ideally, steroids are withdrawn or avoided completely. In tacrolimus-based immunosuppressive regimens, withdrawal of steroids has been successfully performed in 70% of patients, usually by 5 months after transplantation. The effect of this approach on growth has been remarkable, with improvement in the SDS 2 years after transplantation in children younger than 13 years of 3.6 SD in the

---

withdrawn group, as compared with 1.5 SD in the nonwithdrawn group. The rates of acute rejection in the withdrawn group, however, were high, which could adversely affect growth by virtue of a decline in graft function and the need for high-dose steroids to treat rejection. Long-term follow-up of steroidwithdrawn children is required before this regimen can be adopted on a widespread basis.

Growth Hormone

The use of recombinant human growth hormone (rhGH) in pediatric renal transplant recipients significantly improves growth velocity and SDS. Growth velocity almost triples in the first year after starting rhGH therapy, with a slight slowing in the ensuing 2 years of therapy. There is some evidence to suggest that rhGH increases allogeneic immune responsiveness, leading to acute rejection and graft loss in addition to direct adverse effects on graft function. These adverse effects were not observed in the NAPRTCS data. Growth hormone therapy is generally started in prepubertal children at least 1 year after transplantation and continued until catch-up growth is achieved or until puberty ensues. Cyclosporine levels may fall after initiation of rhGH therapy, and the dose should be increased by 10% to 15%.

Allograft Function

A GFR of less than 60 mL per minute per 1.73 m^2 is associated with poor growth and low IGF levels; optimal growth occurs with a GFR greater than 90 mL per minute per 1.73 m^2. Graft function is the most important factor after high corticosteroid dosage in the genesis of post-transplantation growth failure. The immunosuppressive properties of corticosteroids needed to control rejection and preserve kidney function must be balanced against the need to minimize steroids to maximize growth. Thus, an excessive steroid dose leads to impairment of growth and an inadequate dose to impairment of graft function. Administration of high-dose rhGH may induce acceleration of growth even in the presence of chronic graft dysfunction.

Post-transplantation Sexual Maturation

Restoration of kidney function by transplantation improves pubertal development. This

most likely occurs as a result of normalization of gonadotrophin physiology. Elevated gonadotrophin levels and reduced gonadotrophin pulsatility are observed in chronic renal failure, whereas children with successful kidney transplants demonstrate a higher nocturnal rise and increased amplitude of gonadotrophin pulsatility.

Female patients who are pubertal before transplantation typically become amenorrheic during the course of chronic renal failure. Menses with ovulatory cycles usually return within 6 months to 1 year after transplantation, and potentially sexually active adolescents should be given appropriate contraceptive information. Adolescent female transplant recipients have successfully borne children; the only consistently reported neonatal abnormality has been an increased incidence of prematurity. MMF and mycophenolic acid should be held in pregnant female transplant recipients owing to its teratogenic effects on the fetus. Corticosteroids and calcineurin inhibitors can be safely continued. Adolescent males should be made aware that they can successfully father children. No consistent pattern of abnormalities has been reported in their offspring.

Post-transplantation Infections

The reader is referred to Chapter 11 for a full discussion of post-transplantation infections. The spectrum of infections and their presentation may differ

---

somewhat between children and adults, and the following sections focus on these differences. Infection in the immunocompromised child remains the major cause of morbidity and mortality after transplantation and is the most frequent reason for post-transplantation hospitalization.

Bacterial Infections

Pneumonia and urinary tract infections are the most common post-transplantation bacterial infections. Urinary tract infection can progress rapidly to urosepsis and may be confused with episodes of acute rejection. Opportunistic infections with unusual organisms usually do not occur until after the first post-transplantation month.

Viral Infections

The herpesviruses (CMV, herpesvirus, varicella-zoster virus, and EBV) pose a special problem in view of their common occurrence in children. Many young children have not yet been exposed to these viruses, and because they lack protective immunity, their predisposition to serious primary infection is high. The incidence of these infections is higher in children who receive antibody induction therapy and after treatment of acute rejection, and prophylactic therapy is advisable.

Cytomegalovirus. The incidence of CMV seropositivity is about 30% in children older than 5 years of age and rises to about 60% in teenagers. The younger the child, the greater the potential for serious infection when a CMV-positive donor kidney is

transplanted. CMV infection may have the same effect on the course of pediatric transplantation as on adult transplantation, and various strategies have been proposed to minimize its impact. It has been suggested that seronegative children receive only kidneys from seronegative donors; however, given the frequency of seropositivity in the adult population, this restriction would penalize seronegative children with a prolonged wait for a transplant at a critical growing period. CMV hyperimmune globulin, high-dose standard immune globulin, high-dose oral acyclovir, and oral ganciclovir are all potentially valuable therapeutic options. Ganciclovir is effective therapy for proven CMV infection in children. Valganciclovir is under study in pediatric transplantation and has been shown to be effective prophylactic therapy (Table 16.4).

Varicella-Zoster Virus. The most commonly seen manifestation of varicella-zoster virus infection in older pediatric transplant recipients is localized disease along a dermatomal distribution. In younger children, however, primary varicella infection (chickenpox) can result in a rapidly progressive and overwhelming infection with encephalitis, pneumonitis, hepatic failure, pancreatitis, and disseminated intravascular coagulation. It is important to know a child's varicella-zoster antibody status because seronegative children require prophylactic varicella-zoster immune globulin (VZIG) within 72 hours of accidental exposure. VZIG is effective in favorably modifying the disease in 75% of cases. With the development of a new varicella vaccine, it is likely that all seronegative children with ESRD will be appropriately vaccinated.

A child with a kidney transplant who develops chickenpox should begin receiving parenteral acyclovir without delay; with zoster infection, there is less of a threat for dissemination, although acyclovir should also be used. In both situations, it is wise to discontinue azathioprine or MMF until 2 days after the last new crop of vesicles has dried. The dose of other immunosuppressive agents will depend on the clinical situation and response to therapy.

Epstein-Barr Virus. About half of children are seronegative for EBV, and infection will occur in about 75% of these patients. Most EBV infections are clinically silent. PTLD in children, as in adults, may be related to EBV infection in the presence of vigorous immunosuppression (see Chapter 10).

Polyomavirus. Polyomavirus nephropathy is emerging as an important cause of allograft dysfunction and is discussed in Chapters 9, 11, and 14. The virus has been detected in the urine of up to 26% of transplanted children; however, allograft dysfunction as a result of infection appears to be uncommon.

Post-transplantation Antibiotic Prophylaxis

Protocols for post-transplantation antibiotic prophylaxis in children vary from center to center. Most centers use an intravenous cephalosporin for the first 48 hours to reduce infection from graft contamination and the transplant incision. The use of nightly trimethoprim-sulfamethoxazole for the first 3 to 6 months serves as prophylaxis against

Pneumocystis carinii pneumonia and urinary tract infections. Prophylactic oral miconazole (nystatin) minimizes oral and gastrointestinal fungal infections. CMV prophylaxis has been discussed. Children who have undergone splenectomy should be immunized with pneumococcal vaccine and should receive postoperative prophylaxis for both gram-positive and gram-negative organisms, both of which may cause overwhelming sepsis.

Post-transplantation Hypertension and Cardiovascular Disease

Persistent post-transplantation hypertension is a serious problem in children, as it is in adults. More than two thirds of transplanted children treated with cyclosporine are hypertensive, and many require multiple medications for blood pressure control. The differential diagnosis is the same as that for adults. It should be emphasized, however, that late-onset hypertension, especially when accompanied by low-grade fever, is commonly the first sign of acute rejection and may be present before any change in the serum creatinine level. Calciumchannel blockers are generally well tolerated in children and are the agents of choice for blood pressure management.

Concern regarding long-term cardiovascular morbidity and mortality has generally been directed toward the older adult post-transplantation population. Young adults who developed chronic renal disease in childhood must also be considered to be at high risk for cardiovascular morbidity. Risk factors should be addressed in children who will hopefully grow to adulthood with their transplants. Serum cholesterol levels are frequently higher than the 185 mg/dL at-risk level for children with transplants. Dietary measures are appropriate to reduce hyperlipidemia and vascular calcification. Recommendations for the use of statin in children have been made by the American Heart Association (see Sgambat et al).

REHABILITATION OF TRANSPLANTED CHILDREN

Successful reentry into school after transplantation requires coordinated preparation of the child, family or caregivers, classmates, and school personnel. Treatment side effects, social and emotional difficulties, academic difficulties, school resources, and caregiver attitudes all play a role and should be addressed.

Within a year of successful transplantation, the social and emotional functioning of the child and the child's family appears to return to preillness levels. Pretransplantation personality disorders, however, continue to manifest themselves. Within 1 year after transplantation, more than 90% of children attend school, and less than 10% are not involved in any vocational or education programs. Three-year follow-up shows that nearly 90% of children are in appropriate school or job placement. Surveys of 10-year survivors of pediatric kidney

transplants report that most patients consider their health to be good; engage in appropriate social, educational, and sexual activities; and experience a very good or excellent quality of life.

Children carry with them many of the medical consequences of chronic kidney disease into their adult life. Nearly half of adult pediatric transplant recipients are severely short, and more than 25% are obese. Rates of hypertension, orthopedic problems, and cataracts are high. Despite these health problems, most of these adult "survivors" report a good quality of life and successful rehabilitation.

Selected Readings

Bartosh S, Leverson G, Robillard D, et al. Long-term outcomes in pediatric renal transplant recipients who survive into adulthood. Transplantation 2003;76:1195-1200.

Bhakta N, Marik J, Malekzadeh M, et al. Can pediatric steroid-free renal transplantation improve growth and metabolic complications? Pediatr Transplant 2008;12:854-861.

Braun M, Stablein D, Hamiwka L, et al. Recurrence of membranoproliferative glomerulonephritis type II in renal allografts: the North American Pediatric Renal Transplant Cooperative Study Experience. J Am Soc Nephrol 2005;16:2225-2233.

Choy B, Chan T, Lai K. Recurrent glomerulonephritis after kidney transplantation. Am J Transplant 2006;6:2535-2542.

Danziger-Isakov L. Infectious diseases in pediatric transplantation: literature review 2005-2006. Pediatr Transplant 2007;11:595-600.

Dharnidharka VR, Araya CE. Post-transplant lymphoproliferative disease. Pediatric Nephrol 2009;24:731-736.

Ettenger R, Bartosh S, Choi L, et al. Pharmacokinetics of enteric-coated mycophenolate sodium in stable pediatric renal transplant recipients. Pediatr Transplant 2005;6:780-787.

Fine RN. Recurrence of nephrotic syndrome/focal segmental glomerulosclerosis following renal transplantation in children. Pediatr Nephrol 2007;22:496-502.

Hymes LC, Warshaw BL. Sirolimus in pediatric patients: results in the first 6 months

post-renal transplant. Pediatr Transplant 2005;9:520-522.

Kashtan CE. Renal transplantation in patients with Alport syndrome. Pediatr Transplant 2006;10:651-657.

Kranz B, Vester U, Nadalin S, Paul A, et al. Outcome after kidney transplantation in children with thrombotic risk factors. Pediatr Transplant 2006;10:788-793.

Lilien MR, Stroes ES, Op't Roodt J, et al. Vascular function in children after renal transplantation. Am J Kidney Dis 2003;41:684-691.

Loirat C, Fremeaux-Bacchi V. Hemolytic uremic syndrome recurrence after renal transplantation. Pediatr Transplant 2008;23:1957-1972.

Magee JC, Krishnan SM, Benfield MR, et al. Pediatric transplantation in the United States, 1997-2006. Am J Transplant 2008;8:935-945.

Mitznefes M, Kimball T, Border W. Abnormal cardiac function in children after renal transplantation. Am J Kidney Dis 2004;43:721-726.

Neuhaus TJ. Immunization in children with chronic renal failure: a practical approach. Pediatr Nephrol 2004;19:1334-1339.

Ponticelli C, Traversi L, Banfi G. Renal transplantation in patients with IgA mesangial glomerulonephritis. Pediatr Transplant 2004;8:334-338.

Prokai A, Fekete A, Kis E, et al. Post-transplant diabetes mellitus in children following renal transplantation. Pediatr Transplant 2008;12:643-649.

Rianthavorn P, Ettenger R, Malekzadeh M, et al. Noncompliance with immunosuppressive medications in pediatric and adolescent patient receiving solid-organ transplants. Transplantation 2004;77:778-781.

Sarwal M, Pascual J. Immunosuppression minimization in pediatric transplantation. Am J Transplant 2007;7:2227-2235.

Sgambat K, He J, McCarter RJ, et al. Pediatr Transplant 2008;12:796-803.

White CT, Schisler T, Er L, et al. CKD following kidney transplantation in children

and adolescents. Am J Kidney Dis 2008;51:996-1004.

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

17

Psychiatric Aspects of Kidney Transplantation

Itai Danovitch

The psychiatric approach to the transplant recipient can be divided into two major components: the psychosocial evaluation for transplant candidacy and the management of symptoms in post-transplantation patients. This chapter reviews the psychiatric evaluation, diagnosis, and treatment of renal transplant recipients as well as the psycho-social evaluation of living kidney donors. The chapter also includes a concise, symptom-based guide for management of psychiatric symptoms.

BACKGROUND

The relationship between kidney disease and mental illness is bidirectional. Co-occurring psychiatric disorders are associated with poor transplant outcomes. This has been attributed to behavioral factors, such as nonadherence, as well as physiologic factors, such as modification of immunologic and stress responses. Likewise, end-stage renal disease (ESRD) generates vulnerability toward mental illness. In addition to the psychosocial impact of severe medical illness, the internal biochemical milieu of ESRD has been likened to a chronic stress state. Elevated cytokines and inflammatory mediators play a putative role in the pathophysiology of depression. Additionally, peptide and steroid hormones that are ordinarily metabolized by the kidneys circulate at higher levels among patients with ESRD and may contribute to both mood and anxiety disorders.

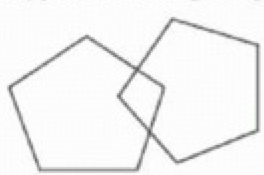
Despite the growing recognition of comorbid psychiatric disorders among patients with ESRD, provision of treatment remains limited. For instance, it has been estimated that although up to 40% of transplant recipients report depressive symptoms, less than 20% of ESRD patients with depression actually receive treatment for it. Although in many cases it may be reasonable for the primary medical team to initiate treatment, the complexity of psychiatric issues in transplant recipients often requires subspecialty care. Within academic medicine, the mental health needs of transplant recipients and donors lie within the scope of transplant psychiatry—a subsection of psychosomatic medicine, which is, in turn, a subspecialty of psychiatry.

EVALUATION

Whether it is for a healthy donor or an ailing patient, psychiatric assessment begins with a comprehensive biopsychosocial evaluation. The evaluating clinician should make sure to inquire about emotions such as mood or anxiety, alterations in perceptions, morbid thoughts about self-harm or harm to others, behavioral symptoms such as adherence, risk taking, and drug use, and environmental and interpersonal stressors. These domains may be moderated by positive prognostic factors such as social supports, insight, spirituality, and the use of adaptive coping mechanisms. Given the prevalence of neurocognitive symptoms, as well as the degree to which they may masquerade as depression, the initial evaluation should include an assessment of cognitive function. A baseline Mini-Mental State Exam (Fig 17.1) is particularly useful as an anchor point against which any subsequent deterioration or improvement of cognition can be compared.

Mini-Mental State Examination

Maximum score	*Score*	
		Orientation
5	____	What is the (year) (season) (date) (day) (month)?
5	____	Where are we: (state) (county) (town or city) (hospital) (floor)?
		Registration
3	____	Name three common objects (e.g., "apple," "table," "penny"): Take one second to say each. Then ask the patient to repeat all three after you have said them. Give one point for each correct answer. Then repeat them until he or she learns all three. Count trials and record.
		Trials: ____
		Attention and calculation
5	____	Spell "world" backwards. The score is the number of letters in correct order. (D__L__R__O__W__)
		Recall
3	____	Ask for the three objects repeated above. Give one point for each correct answer. (Note: recall cannot be tested if all three objects were not remembered during registration.)
		Language
2	____	Name a "pencil" and "watch."
		Repeat the following: "No ifs, ands or buts."
1	____	Follow a three-stage command:
3	____	"Take a paper in your right hand, fold it in half and put it on the floor."
		Read and obey the following:
1	____	Close your eyes.
1	____	Write a sentence.
1	____	Copy the following design.



Total score: ____

FIGURE 17.1 The Mini-Mental State Examination, a useful tool for assessing cognitive function and documenting subsequent decline. Scores of 24 or higher are generally considered normal. (Adapted from Folstein MF. Mini-Mental State Examination [MMSE]. Psychopharm Bull 1988;24:689-692.)

Transplant Donors

The ethical dictum to "do no harm" is the guiding principle in the evaluation of the transplant donor. In parallel to comprehensive medical screening, psychological vulnerability factors should be identified and addressed accordingly. A thoughtful psychiatric interview can uncover subtle coercive factors contributing to a donor's decision, and it is the duty of the transplant team to ensure that these issues are addressed and resolved with the donor in a manner that protects his or her well-being. Among domestic partners, for instance, it is important to inquire about past and present domestic violence. The psychiatric evaluation of prospective donors should characterize the donor's understanding of renal illness and transplant surgery, their relationship to the patient, their expectations of outcome, whether they have anticipated potential economic, social and psychological consequences of the procedure, and finally, how they have arrived at their decision. Additionally, given the skewed risk-benefit equation that characterizes a healthy person submitting to an elective medical procedure to remove an organ, it is critical to evaluate and re-evaluate decision-making capacity. Table 17.1 presents a guide for the psychosocial evaluation of the potential unrelated transplant donor. Table 17.2 suggest characteristics that serve as risk factors for, or protective factors against, poor psychosocial outcomes in living kidney donors, emphasizing factors of heightened importance for unrelated donors (see Chapter 6).

TABLE 17.1 Required Components of the Psychosocial Evaluation of Living Unrelated Kidney Donors

History and current status: Obtain standard background information regarding such areas as the prospective donor's educational level, living situation, cultural background, religious beliefs and practices, significant relationships, family psychosocial history, employment, lifestyle, community activities, legal offense history, and citizenship.

Capacity: Ensure that the prospective donor's cognitive status and capacity to comprehend information are not compromised and do not interfere with judgment; determine risk for exploitation.

Psychological status: Establish the presence or absence of current and prior psychiatric disorder, including but not limited to mood, anxiety, substance use, and personality disorders. Review current or prior therapeutic interventions (counseling, medications); physical, psychological, or sexual abuse; current stressors (e.g., relationships, home, work); recent losses; and chronic pain management. Assess repertoire of coping skills to manage previous life or health-related stressors.

Relationship with the transplant candidate: Review the nature and degree of closeness (if any) to the recipient, such as how the relationship developed and whether the transplant would impose expectations or perceived obligations on the part of either the donor or the recipient.

Motivation: Explore the rationale and reasoning for volunteering to donate, that is, the “voluntariness,” including whether donation would be consistent with past behaviors, apparent values, beliefs, moral obligations, or lifestyle, and whether it would be free of coercion, inducements, ambivalence, impulsivity, or ulterior motives (e.g., to atone or gain approval, to stabilize self-image, to remedy psychological malady).

Donor knowledge, understanding, and preparation: Explore the prospective donor's awareness of any potential short- and long-term risks for surgical complications and health outcomes, both for the donor and the transplant candidate; recovery and recuperation time; availability of alternative treatments for the transplant candidate; and financial ramifications (including possible insurance risk). Determine that the donor understands that data on long-term donor health and psychosocial outcomes continue to be sparse. Assess the prospective donor's understanding, acceptance, and respect for the specific donor protocol, including willingness to accept potential lack of

communication from the recipient and willingness to undergo future donor follow-up.

Social support: Evaluate significant other, familial, social, and employer support networks available to the prospective donor on an ongoing basis as well as during the donor's recovery from surgery.

Financial suitability: Determine whether the prospective donor is financially stable and free of financial hardship; has resources available to cover financial obligations for expected and unexpected donation-related expenses; is able to withstand time away from work or established role, including unplanned extended recovery time; and has disability and health insurance.

From Dew MA, Jacobs CL, Jowsey SG, et al. Guidelines for the psychosocial evaluation of living unrelated kidney donors in the United States. Am J Transplant 2007;7:1047-1054, with permission.

Transplant Recipients

From pretransplantation screenings, to capacity assessments, to symptomfocused evaluations, the psychiatric assessment of transplant recipients varies a great deal depending on the goal at hand. The evaluation should be framed according to the reason for the assessment, and the patient needs to understand the examiner's intentions, whether it is to address psychiatric symptoms or as a general screening component of the pretransplantation assessment.

The evaluation of transplant recipients is a psychosomatic evaluation in the broadest sense of the term. The clinician must make an effort to differentiate psychiatric presentations of renal illness from somatic manifestations of psychiatric illness. For instance, somatic symptoms of uremia, such as insomnia, anorexia, lethargy, can be mistaken for depression (Table 17.3). Similarly, immunosuppressive medications such as steroids can induce wideranging neuropsychiatric presentations. Although psychiatric measures can be helpful, many have called into question the validity of scales that were designed to detect psychopathology in the general population, and efforts are

ongoing to develop reliable, valid, and clinically feasible measures for targeted use in patients with advanced renal disease. Psychosocial eligibility determinations are controversial and have largely been determined through consensus guidelines. The Canadian Society of Transplantation has issued evidence-based guidelines on psychosocial eligibility for kidney transplantation (Table 17.4).

Psychological Impact

It is simply not possible to overstate the profound psychological impact of kidney transplantation. Whereas all forms of illness undermine the fantasy of invulnerability that buoys the "sense of self," the significance of a failing organ system requiring replacement by donation from another person is an enormous challenge for the psyche and one that can only be understood when framed within the background of social, religious, spiritual, ethnic, and cultural perspectives. Add in the emotional strain of chronic dialysis, the uncertainty involved in waiting for a transplant, the disfigurement that can occur with chronic renal disease, and the repercussions of powerful immunosuppressive medications and you have the makings for an upheaval of the mind as well as the body. The fact that some people manage to navigate these challenges without becoming symptomatic is a testament to protective factors such as resilience and psychosocial support.

Any psychiatric assessment, even if it only does so indirectly, must pay heed to how the above dynamics are integrated and psychologically metabolized. Where the evaluator notes areas of resistance, discomfort, embarrassment, or demoralization, a brief supportive exploration may be indicated to characterize what thoughts or feelings are disturbing, and why. The sheer existential challenge of life suddenly redefined in terms of "survival years" may lead patients to call into question firmly held beliefs. We live in a culture that places exceeding value on body image, and the physical changes that can develop may further undermine previously stable parts of identity. Marital discord is highly prevalent among patients with ESRD, a particular concern because investigations of social support have suggested that "perception" of support may be more important than support itself as a predictor of survival. In some cases, there may be a vital role for individual therapy, group therapy, or family therapy.

TABLE 17.2 Characteristics Serving as Risk Factors for, or Protective Factors I Against, Poor Psychosocial Outcomes in Living Kidney. Donors ***Factors of Heightened Importance for Unrelated Donors In Italics***

Lower Risk or Protective	Higher Risk

No diagnosable psychiatric disorder or significant psychiatric symptoms	Significant past or ongoing psychiatric symptoms or disorders
No evidence of substance abuse	Substance abuse or dependence
Financial resources that could cover unexpected costs	Limited financial capacity to manage donation (lost wages, travel, job concerns)
Health insurance	Lack of health insurance
Knowledgeable about potential risk and benefits to donor or recipient	Limited capacity to understand donor risks and recipient benefits and alternatives
	Increased medical risks (e.g., chronic pain conditions)
Little to no ambivalence about proceeding with donation, *realistic expectations about the donation experience, and potential recipient outcomes*	Marked ambivalence about donating, *or unrealistic expectations about the donation experience and potential recipient outcomes*
	Motives reflecting desire for recognition, or

Altruistically motivated; a history of medical altruism	*a desire to use the donation to develop personal relationships (e.g., desire for publicity, desire for a relationship with an individual or with treatment providers)*
History of reasonable adaptation to typical life stressors, *no recent significant losses or stressors*	*Multiple family stressors, obligations, or concerns* Subordinate relationship (e.g., employee or employer) or other evidence of coercion Evidence of, or expectation of, secondary gain (e.g., avoidance of military duty, financial support from recipient)
Support from family for donation; knowledge by family of possible donation	Poor relationship with family; poor family support for donation

From Dew MA, Jacobs CL, Jowsey SG, et al. Guidelines for the psychosocial evaluation of living unrelated kidney donors in the United States. Am J Transplant 2007;7:1047-1054, with permission.

TABLE 17.3 Symptom Parallels Between Depression and Uremia

Uremia	**Depression**

Encephalopathy	Depression
	Poor concentration
Anorexia	Decreased appetite
Sleep apnea	Insomnia
Anemia	Decreased energy
Volume overload	
Neuropathy, arthropathy	Somatization
Restlessness, akathisia	Anxiety
	Guilt
	Suicidality

TABLE 17.4 Canadian Society of Transplantation Consensus Guidelines on Psychosocial Eligibility for Kidney Transplantation

- Given the importance of adherence to therapy in transplant outcomes, all patients should have a pretransplantation psychosocial evaluation by an experienced competent individual to assess for:
  - Cognitive impairment (grade C)
  - Mental illness (grade C)
  - Nonadherence to therapy, laboratory monitoring, or follow-up (grade C)
  - Drug or alcohol abuse (grade C)
- Cognitive impairment is not an absolute contraindication to kidney transplantation (grade B). However, particular care must be taken to ensure that informed consent can be obtained and that a support system is in place to ensure adherence to therapy and patient safety.
- A history of psychiatric illness is not an absolute contraindication for kidney transplantation. Such patients should be assessed to ensure that they are capable of giving informed consent and adhering to therapy (grade B).

- Patient nonadherence to therapy is a contraindication to kidney transplantation, given the use of immunosuppressive agents with a narrow therapeutic window, the impact of nonadherence to therapy on risk for acute rejection and premature graft loss, and the scarcity of donor organs (grade A). Patients should be informed of the importance of adherence to therapy as well as the number of medications, clinic visits, and blood work required before transplantation (grade B).

- Kidney transplantation should be delayed until patients have demonstrated adherence to therapy (attendance for dialysis and compliance with medications) for at least 6 months (grade C).

- Kidney transplantation should be delayed until the patient has demonstrated freedom from substance abuse for at least 6 months (grade C).

The strength of evidence supporting each recommendation was graded using the system developed by the Canadian Task Force on Preventive Health Care as follows:

Grade A—There is good evidence to support.

Grade B—There is fair evidence to support.

Grade C—The existing evidence is conflicting, but other factors may influence decision making.

Grade D—There is fair evidence to recommend against.

Grade E—There is good evidence to recommend against.

From Knoll G, Cockfield S, Blydt-Hansen T, et al. Canadian Society of Transplantation: Consensus guidelines on eligibility for kidney transplantation. CMAJ 2005;173:S1, with permission.

Adherence

The way in which an individual copes often has the antecedents of the challenges that they will face. Most patients adhere to medication regimens very closely in the days after transplantation, but as the reality of living with a chronic illness sets in, adherence may wane. Nonadherence is defined as failure to follow treatment recommendations (nutritional, pharmacologic, or lifestyle) despite cognitive understanding of their significance. Misunderstandings resulting from language barriers, education, inadequate informed consent, or alterations in cognition are separate phenomena. An initial assessment must attempt to characterize how the patient has coped with difficulties in the past as well as the present. What emotional strategies have they used? Do they have, and make use of, social supports? Also, how do they understand their current situation? What challenges do they anticipate? What kinds of defense mechanisms do they use?

Defense mechanisms are the mind's tools for warding off the anxiety associated with unwanted thoughts or feelings. Adaptive defenses, like humor, diffuse tension while facilitating a clear view of reality. Maladaptive defenses, like denial, dispel tension by distorting or avoiding unwanted aspects of reality. Avoidance and distortion are problematic because they prevent a “working through” of the stressor. Chronic use of any defense mechanism can become problematic if it prevents adherence to the necessary medical regimen. Just as alcoholics in denial miss the chance to address their drinking before it destroys their life, transplant recipients' denial may lead them to dismiss the importance of their doctor's recommendations about an emerging issue in their illness.

In addition to maladaptive defenses, the hopelessness engendered by mood disorders such as depression can undermine a patient's adherence. In fact, depression is associated with a threefold increase in nonadherence. In the past, psychiatric illness was often cited as a contraindication to transplantation because of the perceived risks

of nonadherence. But characterizing these problems and addressing them early on ensures that patients with mental disorders will not be penalized for their psychiatric illness. Specifically, identifying the precursors to nonadherence is critical because it paves the way for initiating interventions to alleviate symptoms, improve morale, reduce hopelessness, and reinforce coping strategies.

Psychopharmacology and Drug Interactions

Determining appropriate psychotropic agents requires an understanding of the pharmacokinetic and pharmacodynamic changes that occur before and after receipt of a kidney. Renal excretion, metabolism, medication dialyzability, protein binding, competitive inhibition, and induction of P-450 systems must be taken into account. Moreover, a number of antirejection medications have important adverse neuropsychiatric effects (Table 17.5). Even in the absence of overt medication interactions, protracted medical illness may contribute to a general state of neuropsychiatric vulnerability to adverse effects, whereby there is greater sensitivity to the mood, behavior, and cognitive sequelae of psychotropic medications. Overall, patients with renal illness need to be monitored more closely than their counterparts without renal illness, and the proviso to “start low and go slow” is the presiding guideline for determining titration schedules.

TABLE 17.5 Adverse Neuropsychiatric Effects of Renal Transplant Medications

Medication	Adverse Neuropsychiatric Reactions
Cyclosporine	Anxiety, restlessness, delirium, visual hallucinations, paresthesias, tremor, seizures, ataxia, cortical blindness
Tacrolimus	Insomnia, tremor, delirium, paranoia, akinetic mutism, leukoencephalopathy
Sirolimus	

Penicillins	Seizures, delirium, perceptual disturbances
Fluoroquinolones	
Lamivudine	Headache, insomnia, fatigue
Ribavirin	Irritability, depression, suicidality, fatigue, insomnia, anxiety
Acyclovir, valacyclovir	Delirium, depression, perceptual disturbances
Ganciclovir, valganciclovir	Headache, seizures, nightmares, perceptual disturbances
Prednisone	Affective instability—ranging from depression to mania, psychosis, delirium, impaired cognition

Adapted from Hafliger S. A primer on solid organ transplant psychiatry. In Wyzynski AA, ed. Manual of Psychiatric Care for the Medically Ill. Washington, DC: American Psychiatric Association, 2005.

A few general principles inform the psychopharmacologic approach to transplant recipients, and these can be framed as questions to be addressed when starting any new medication:

1. What is the volume of distribution? Ascites and edema can lead to increases in volume of distribution, requiring higher dosing of medications to avoid dilution. Conversely, dehydration and muscle wasting may dictate decreased doses to avoid toxicity.

2. How will the medication be metabolized? Are there competitive inhibitory or inductive interactions at P-450 systems? P-450 induction can result in subtherapeutic levels of vital immunosuppressant medications, whereas inhibition can contribute to rapid toxicity.

3. How will the medication be eliminated? Many hepatically metabolized medications still require renal clearance, and impairment of renal function can result in accumulation of metabolites.

4. Is the medication dialyzable? Dialysis almost completely removes hydrophilic medications (such as lithium and Neurontin) but not lipophilic medications (such as most serotonin reuptake inhibitors). Before a medication is prescribed to a patient receiving dialysis, its dialyzability must be determined. Medications that are dialyzed can usually be dosed after dialysis. Medications that are not dialyzed may need to be dosed at a substantial decrement.

5. What is the therapeutic window? Medications such as lithium have intrinsic renal toxicity and pose a marked increased risk for toxicity if there is deterioration in renal function.

6. What is an appropriate starting dose? Most experts agree that even in the absence of any anticipated pharmacokinetic or pharmacodynamic complications, initial starting doses should be reduced by a third.

MANAGEMENT OF PSYCHIATRIC SYMPTOMS IN TRANSPLANT RECIPIENTS

What follows is a symptom-based guide to treatment. With the exception of acute agitation, in most cases, immediately correctable medical contributors need to be addressed before treatment is initiated. Also, given the rapid evolution of pharmacologic agents, new drugs should be checked for interactions against the remainder of each patient's regimen.

Delirium and Agitation

When severe illness overwhelms the brain's capacity to maintain homeostasis, the result is delirium, an acute syndrome characterized by impaired cognition, fluctuating level of consciousness, inattention, and behavioral dysregulation. The behavioral manifestations of delirium may incline some to suspect a psychiatric disorder, but it is critical not to be misled. Psychiatric management of delirium focuses on controlling symptoms, whereas the mainstay of treatment depends on the diagnosis and treatment

of the underlying medical cause or causes. That being said, the psychiatric consultant should assist the primary team in developing a comprehensive differential diagnosis (Table 17.6).

TABLE 17.6 Common Causes of Delirium in Kidney Transplant Recipients

Acute graft failure
Drug toxicity
Drug withdrawal
Uremia
Infection
Ischemic stroke
Intracerebral hemorrhage
Metabolic derangement

There are two arms to the management of agitation. The nonpharmacologic approach includes frequent reorientation, decreasing aversive stimuli, providing familiar comforts, and careful use of soft restraints. For patients who do not have family available to support them, a 24-hour sitter can help to comfort, orient, and psychologically ground the patient, resulting in a significant calming effect (Table 17.7).

The pharmacologic approach to delirium has recently been under re-evaluation owing to concerning epidemiologic data suggesting an association between antipsychotic medications and mortality. Consequently, nonpharmacologic interventions should always be maximized, and a risk-benefit assessment should take place before initiation of antipsychotics. However, in many cases of delirium, the increased risk for mortality associated with antipsychotic medications is less than the imminent risk for harm arising from agitated behavior. Among antipsychotic medications, the best evidence rests with haloperidol. Initial doses should range from 0.5 to 2 mg orally or parenterally every 2 to 4 hours, titrated to reduction in the agitated behavior. Frequent follow-up, assessment of extrapyramidal symptoms, and monitoring of the QTc interval and drug-drug interactions are vital to minimize toxicity, particularly when high doses are required. The antipsychotic should be stopped once agitation remits. For patients requiring frequent dosing, a standing regimen may be instituted to provide a baseline of prophylaxis. Among the atypical antipsychotics, quetiapine and risperidone are frequently used, although the risk-benefit equation with these agents is generally less optimal than that of haloperidol.

Mood

Depression is widespread among transplant recipients. Because most trials exclude patients with renal failure, there is little evidence to direct choice of antidepressant medications. However, studies of serotonin reuptake inhibitors in medically ill populations suggest that they are superior to placebo, and overall they are well tolerated. This, combined with the known toxicities of older antidepressants such as monoamine oxidase inhibitors and tricyclic antidepressants, means that unless patients are shown to be treatment refractory, serotonin reuptake inhibitors should be maximized first. Herbal remedies are generally avoided owing to inadequate dosing regulations, and St. John's Wort is particularly contraindicated because of its documented induction of P-450 systems and known interactions with cyclosporine.

When starting antidepressants in patients with renal disease, assuming there are no known interactions (Table 17.8), it is still generally advisable to lower the starting dose by at least one third. Starting at low dosages and titrating slowly minimizes the likelihood of common adverse effects such as nausea,

---

restlessness, headache, grogginess, and sexual dysfunction. Patients should be advised that it takes about 4 weeks for medications to exert their full benefit at any particular dose range.

TABLE 17.7 Environmental Interventions in Treating Patients with Delirium

Provide Support and Orientation

Communicate clearly and concisely; give repeated verbal reminders of the day, time, location, and identity of key persons, such as members of the treatment team and relatives.

Provide clear signposts to patient's location, including a clock, calendar, and chart with the day's schedule.

Place familiar objects from patient's home in the room.

Ensure consistency in staff (e.g., a key nurse).

Use television or radio for relaxation and to help the patient maintain contact with the outside world.

Involve family members and caregivers to encourage feelings of security and orientation.

Provide an Unambiguous Environment

Simplify care area by removing unnecessary objects; allow adequate space between beds.

Consider using private room to aid rest and avoid extremes of sensory experience.

Avoid using medical jargon in patient's presence because it may encourage paranoia.

Ensure that lighting is adequate; provide a 40- to 60-watt nightlight to reduce misperceptions.

Control sources of excess noise (e.g., staff, equipment, visitors); aim for fewer than 45 dB during the day and fewer than 20 dB during the night.

Maintain room temperature between 21.1°C (69.98°F) and 23.8°C (74.8°F).

Maintaining Competency

Identify and correct sensory impairments; ensure patients have their glasses, hearing aids, and dentures. Consider whether interpreter is needed.

Encourage self-care and participation in treatment (e.g., ask patient for feedback on pain).

Arrange treatments to allow maximum periods of uninterrupted sleep.

Maintain activity levels: ambulatory patients should walk 3 times daily; nonambulatory patients should undergo full range of movement exercise for 15 minutes 3 times daily.

From Meagher DJ. Delirium: optimising management. BMJ 2001;322:146, with permission.

For patients with a history of bipolar disorder, mood stabilization often presents a challenge on account of the unfavorable adverse-effect profiles of approved medications. Carbamazepine is an excellent mood stabilizer, but its multifold medication interactions make it difficult to use. Lamotrigine is well tolerated but is not an adequate mood stabilizer for patients with a history of bipolar disorder type I. The two most commonly used agents are valproic acid and lithium. Valproic acid is hepatically metabolized with relatively minimal renal clearance. Valproic acid is titrated according to serum level, with the caveat that reduced protein binding affects serum level. Lithium is contraindicated in acute renal failure owing to its tubulointerstitial toxicity, but it may be used in chronic renal failure. Specific guidelines are available to estimate dosing based on glomerular filtration rate, and frequent monitoring of blood levels is vital to keep the medication within the therapeutic window. Because lithium is excreted exclusively through the kidneys, and it is 100% dialyzed, patients

should be dosed after each episode of dialysis. Lithium levels should be acquired before each subsequent hemodialysis until steady state is reached, at which point levels can be monitored monthly. Finally, a number of atypical antipsychotics have been approved as mood stabilizers, and characteristics of these medications are reviewed in Table 17.8.

TABLE 17.8 Selected Psychotropic Medicati

Class	Drug	Normal Dose	Approximate Percentage Protein Bound	Normal Half-Life	Ha in Di
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram	20-60 mg	80	33-37 hr	43
	Escitalopram	10-30 mg	56	22-32 hr	—
	Paroxetine	20-60 mg	95	17-25 hr	11
	Sertraline	50-200 mg	98	24 hr	42
	Fluoxetine	20-60 mg	95	24-96 hr	40

Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Duloxetine	60-120 mg	90	12 hr	—
	Venlafaxine	37.5-225 mg	30	4 hr	6-
Tricyclic antidepressants (TCAs)	Amitriptyline	50-150 mg	—	32-40 hr	32
	Clomipramine	100-250 mg	97	19-37 hr	—
	Imipramine	25 mg every 8	—	6-20 hr	—

		hr			
	Nortriptyline	50-150 mg	93	18-93 hr	15
Other antidepressants	Bupropion	100-450 mg	85	10-21 hr	—
	Nefazodone	50-150 mg every 12-24 hr	99	3-5 hr	3-
	Trazodone	50-400 mg	90	4-11 hr	—
	Mirtazapine	15-45 mg	85	20-40 hr	—
Mood stabilizers	Valproic acid	15-60 mg/kg	80-90	6-17 hr	—

	Lithium	900-1200 mg	—	14-28 hr	4(
	Lamotrigine	100-200 mg	55-56	13-30 hr	4
	Carbamazepine	800-1200 mg twice daily	76	12-17 hr	N su ch
Typical antipsychotics	Haloperidol	1-2 mg every 8-12 hr	90	14-26 hr	1
	Chlorpromazine	50-400 mg/day		11-42 hr	11

Atypical antipsychotics	Quetiapine	25-750 mg	83	6 hr	—
	Aripiprazole	10-45 mg	99	75-146 hr	—
	Ziprasidone	20-80 mg twice daily	99	7 hr	—
	Risperidone	0.5-3 mg twice daily	90	3-30 hr	25
	Olanzapine	5-20 mg	93	32-38 hr	32

	Clozapine	12.5-450 mg	97	8-12 hr	—
Benzodiazepines	Lorazepam	0.5-2 mg	85	9-16 hr	32
	Clonazepam	0.25-1 mg	85	18-80 hr	—
	Alprazolam	0.25-1 mg	80	9-19 hr	9-
	Temazepam	15-30 mg	96	4-10 hr	—
	Diazepam	5-10 mg	98	92 hr	37

Nonbenzodiazepine sedatives	Zolpidem	5-10 mg	92	2-3 hr	4-
	Zaleplon	5-20 mg	60	1 hr	—
Substance dependence medications	Naltrexone	50-150 mg	21	5-10 days	—
	Disulfiram	250-500 mg	96	12 hr	—
	Acamprosate	333-666 mg 3 times daily	Negligible	3.2-13 hr	—
	Topamax	100-200 mg	9-41	18-24 hr	—

	Buprenorphine	2-32 mg	96	1.2-7.2 hr	—
	Methadone	20-200 mg	71-88	23-50 hr	—
Other medications	Neurontin	100-1200 mg 3 times daily	<3	5-7 hr	6.
	Modafinil	200-400 mg	60 7.5-15 hr	22 hr	—
	Buspirone	10-30 mg twice daily	86	2.4-2.7 hr	—

CrCI, creatinine clearance; ESRD, end-stage renal disease.

Adapted from Brady HR, Wilcox CS, eds. Therapy in Nephrology and Hypertension: A ed. Philadelphia: WB Saunders, 2003. Also adapted from MicroMedex.

Anxiety

Anxiety is prevalent across patients with severe medical illness and has a substantial negative impact on quality of life. Anxiety itself is a symptom, although when combined with other psychopathology and loss of function, it may be a part of a full-fledged psychiatric disorder. Counseling, support groups, and psychotherapy are vital psychosocial interventions to reduce anxiety. For patients with panic disorder (a common diagnosis in ESRD), there is strong evidence that both cognitive behavioral therapy and psychoanalytically oriented psychodynamic psychotherapy are effective in achieving remission. The use of one type of therapy or another depends in large part on available clinical resources, funding, and patient preference.

The pharmacologic approach to anxiety disorders rests largely on the judicious use of serotonin reuptake inhibitors. Unfortunately, the serotonergic-based anxiolytics require 4 to 6 weeks to exert their full effects, and sometimes during that interval, they actually exacerbate anxiety. One solution is to use a “bridging dose” of a benzodiazepine to provide immediate symptom relief. For this purpose, long-acting benzodiazepines, such as clonazepam, 0.5 mg twice daily, are preferred because their pharmacokinetics makes them less reinforcing than short-acting agents, and using them on a standing basis minimizes some patient's inclination to self-medicate a wide range of symptoms. For acute phobic anxiety related to procedures or interventions, lorazepam, 1 mg every 8 hours, is effective and is favorable because it undergoes hepatic metabolism without active metabolites.

Psychosis

Throughout much of the history of organ donation, patients with psychotic disorders such as schizophrenia, schizoaffective disorder, and severe bipolar disorder were excluded because of concern about their ability to adhere to complicated postoperative treatment regimens. More than 29% of U.S. Medicare patients on dialysis have been diagnosed with a psychotic disorder, however, and recognition that many patients with severe psychotic disorders can be perfectly adherent when appropriate supports are put in place has led to an incremental increase in organ allocation to this population. The physiologic and psychological stress of ESRD places the patient at high risk for decompensation, but a close relationship between psychiatric and medical teams can facilitate a smooth treatment course.

For patients without a history of a psychotic disorder, a new-onset psychotic symptom represents delirium until proven otherwise. A comprehensive workup, including head imaging and evaluation of metabolic, endocrinologic, infectious, autoimmune, and pharmacologic factors must be undertaken. For patients with a history of substance

abuse, particularly stimulants, a urine toxicology screen can be used to "rule in" substance-induced psychotic disorders.

Insomnia

Insomnia is commonplace among medically ill patients, and the many discomforts endured by patients with ESRD frequently lead to impairments in sleep. Nevertheless, treatment of insomnia begins with psychoeducation about the importance of sleep hygiene. Patients should avoid stimulating agents such as caffeine after noon, and they should promote a relaxing environment in the hour before going to sleep. Underlying psychiatric (i.e., depression, anxiety) and

medical (i.e., sleep apnea, hyperthyroidism) causes of insomnia must be identified because their treatment will resolve the symptom.

Table 17.8 describes the profile of common sedative hypnotic agents. Benzodiazepines and benzodiazepine-like medications are generally avoided because they disturb sleep architecture (leading to decreased delta-wave restorative sleep) and induce dependence. However, they are particularly helpful for patients with initial insomnia (difficulty falling rather than staying asleep), and used judiciously, they can provide substantial symptom relief. The medications mirtazapine and trazodone were developed as antidepressants. Their inclination to cause prominent sedation at low doses, coupled with their general tolerability, has led them to be used as effective sedatives more often than their use as antidepressants (the antidepressant dosages for these medications is multifold higher than their sedative dose range). Patients should be advised about the risk for weight gain with mirtazapine and of the rare but important risk for priapism with trazodone. Restless leg syndrome is a common cause of insomnia among renal patients, and addressing this is often sufficient to improve sleep.

Addiction and Pain

The strict requirements for organ allocation mean that most patients are excluded from transplantation if they are actively abusing drugs or alcohol. However, some previously sober individuals relapse under the stress of kidney transplantation, and still others succumb to self-medication of symptoms with alcohol and prescription or illicit drugs. The stigma associated with drug addiction leads many patients with a substance abuse history to expect misjudgment by medical professionals, and unfortunately, these expectations often frame the nature of their interactions. In turn, well-meaning but frustrated health care providers may become demoralized about their inability to help these patients and seek instead to discharge or minimize interaction with them. Thus, a cycle is perpetuated, in which these ill patients receive less rather than more treatment.

Substance abuse treatment can be divided into three groupings: self-help, psychosocial therapies, and psychopharmacologic interventions. Self-help groups such as alcoholics

anonymous (AA) are free, ubiquitous, and offer vital support to those patients who are sufficiently self-motivated. Individual counseling or therapy can offer vital skills to patients who have been unable to stop using alcohol or drugs on their own. For patients whose lives are chaotic, or whose ambivalence prevents meaningful engagement in self-help groups, a structured intensive outpatient program or residential treatment may be necessary. Psychopharmacologic interventions are used first to assist with detoxification and second to assist patients' efforts to maintain sobriety. Table 17.8 reviews medications with U.S. Food and Drug Administration approval for drug or alcohol dependence. These drugs typically improve rates of sobriety by either reducing craving, diminishing the reinforcing effects of drug use, or pharmacologically replacing the drug of abuse with a legal and less harmful agent.

The issue of pain is addressed here because when it occurs in the context of a current or past history of addiction, it can present a number of challenges. Patients manifesting drug-seeking behavior may simultaneously suffer from somatic pain. In fact, the term *pseudoaddiction* was coined to characterize the appearance of drug-seeking behavior among patients who simply have undertreated pain. Health care providers must walk the fine line of not undertreating pain while addressing manifest abuse behaviors. Putting aside moral or ethical considerations about drug use, abuse behaviors are concerning because they invariably lead down a path of nonadherence and decompensated renal disease. Management of pain and addiction often requires an interdisciplinary approach,

---

with a pain management service explicitly managing pain medications in collaboration with a psychiatric or psychological service to address abuse behaviors. Interventions to help this population include: maximizing use of nonopioid analgesics; minimal use of sedative hypnotic medications that induce dependence; preferential use of long-acting opioids in lieu of highly reinforcing short-acting agents; establishment of a clear treatment contract; and evaluation and treatment of underlying psychiatric disorders that compel self-medication.

Interpersonal Difficulties and Nonadherence

The manifold stresses of ESRD extract a substantial toll on patients and their families alike. The tumultuous path from renal disease to renal failure, dialysis, and transplantation is beset with stress and disappointments. Family and friends may have mixed feelings about finding themselves in the unanticipated role of “caregiver.” Even the strongest of relationships can waiver in the face of such challenges, and relationships with preexisting problems often face a particularly turbulent course. Thus, patients must contend with both intrapersonal (having to do with their internal emotional life) and interpersonal (having to do with their relationships with others) difficulties. The pretransplantation psychosocial evaluation is intended to anticipate some of these challenges and initiate a plan to address them, but there is no way to fully defray the burden that patients have to bear.

A full discussion on the evaluation of interpersonal problems among the medically ill is beyond the scope of this chapter (for a comprehensive review, see Groves and Muskin in “Selected Readings”). Unfortunately, one of the common manifestations of interpersonal problems is nonadherence. Presuming that neuropsychiatric etiologies of nonadherence have been appropriately ruled out, the following psychological dimensions should be considered: Is it possible that nonadherence is the patient's way of dealing with loss of function, in which case, rather than accept unnerving feelings of impotence, the patient may maintain a pretense of imperviousness? Is it possible that the patient feels helpless, in which case, the patient may assert his or her autonomy by exerting control over treatment providers? And finally, is it possible that the patient is projecting anger about the illness at the treatment team, and thus rejecting the team's recommendations? These are just a few examples of interpersonal causes of nonadherence, but each one informs a different therapeutic approach. To the patient who feels ashamed about loss of function, supportive, empathic comments can make them feel at ease. To the patient who feels helpless, identifying ways in which the patient can exert positive control over their condition may restore a sense of autonomy and independence. And to the patient who expresses anger, compassionately exploring the patient's thoughts might help the patient process and work through underlying sadness.

CONCLUSIONS

ESRD is a paradigmatic biopsychosocial illness. The profound physiologic dysregulation that characterizes transplant recipients is paralleled by enormous stress in the psychological and social domains. Unfortunately, despite widespread acknowledgement of the morbidity, mortality, and social costs incurred as a result of psychiatric disorders, there are few randomized controlled trials informing pharmacologic and psychosocial interventions. The field would greatly benefit from standardization of measures used to screen and diagnose psychiatric disorders in transplant recipients, and trials of interventions should be tied to concrete clinical end points such as mortality, symptom severity, and quality of life. But most importantly, in a field in which physiologic and psychological illnesses frequently intersect to create complicated presentations and

clinical dilemmas, the active collaboration of trained health care providers is vital to ensure that patients receive high-quality integrated care.

Selected Readings

Cohen LM, Tessier EG, Germain MJ, Levy NB. Update on psychotropic medication use in renal disease. Psychosomatics 2004;45:34-48.

Cukor D, Cohen SD, Peterson RA, Kimmel PL. Psychosocial aspects of chronic disease:

ESRD as a paradigmatic illness. J Am Soc Nephrol. 2007;18:3042-3055.

Dew MA, Jacobs CL, Jowsey SG, et al. Guidelines for the psychosocial evaluation of living unrelated kidney donors in the United States. Am J Transplant 2007;7:1047-1054.

Dobbels F, Skeans MA, Snyder JJ, et al. Depressive disorder in renal transplantation: an analysis of Medicare claims. Am J Kidney Dis 2008;51:819-828.

Groves M, Muskin PR. Psychological responses to illness. In Levenson JL, ed. The American Psychiatric Publishing Textbook of Psychosomatic Medicine. Arlington, VA: American Psychiatric Publishing, 2005.

Kimmel PL. Depression in patients with chronic renal disease: what we know and what we need to know (review). J Psychosom Res 2002;53:951-956.

Kimmel PL, Cukor D, Cohen SD, Peterson RA. Depression in end-stage renal disease patients: a critical review (review). Adv Chronic Kidney Dis 2007;14:328-334.

Rabindranath KS, Butler JA, MacLeod AM, et al. Physical measures for treating depression in dialysis patients. Cochrane Database Syst Rev 2005;18:CD004541.

Rabindranath KS, Daly C, Butler JA, et al. Psychosocial interventions for depression in dialysis patients. Cochrane Database Syst Rev 2005;3:CD004542.

Skotzko CE, Strouse TB. Solid organ transplantation. In Wise MG, Rundell JR, eds. The American Psychiatric Publishing Textbook of Consultation-Liaison Psychiatry: Psychiatry in the Medically Ill. Arlington, VA: American Psychiatric Publishing, 2001.

Surman O, Cosimi A, DiMartini A. Psychiatric care of patients undergoing organ transplanation. Transplantation 2009;87:1753-1761.

Wyszynski AA, Wyszynski B, eds. Manual of Psychiatric Care For the Medically Ill. Arlington, VA: American Psychiatric Publishing, 2004.

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

18

Ethical and Policy Issues in Organ Transplantation

Jeffrey P. Kahn

Since the first successful solid organ transplants, the field of organ transplantation has been confronted with ethical and policy issues just as it was confronted with technical and medical issues. In fact, transplantation is one of the few areas of medicine in which the ethical and policy issues receive such primary and sustained attention. This is due to a combination of factors, including the ethical issues inherent in removing body parts from one person to give to another, the issues raised by the chronic shortage of a scarce life-saving resource and how it should be distributed, and the ways in which a society should address these and other questions as matters of public policy, including law.

ETHICAL ISSUES IN TRANSPLANTATION OF DECEASED DONOR ORGANS

In the past, ethical and policy issues in kidney transplantation focused on the donation and allocation of organs from deceased donors because they represented most available kidneys. The focus on the supply of organs from deceased sources was influenced by advances on two fronts. First, the ability to successfully perform allografts meant that the demand for organs to transplant increased dramatically. Second, discussion and debate about definitions of death and making decisions at the end of life inevitably turned to include the procurement of solid organs from deceased donors. Therefore, the policy environment and ethics debate focused on two main issues: when is it acceptable to remove organs from patients after they have died, and how should we allocate the very scarce resource that these organs represent?

Obtaining organs from deceased donors has been governed by strict rules (both policies and law) created to ensure that important ethical principles are respected. These include the primacy of respect for individual autonomy and making medical decisions that are in the best interests of patients. In application, these principles affect how we should think about the care of patients at the end of life, making sure to respect the decisions of individuals or their proxies about donation after death.

When it comes to the medical care of patients at the ends of their lives, it is crucial

that decisions about care are not compromised or influenced by motives to procure organs for transplant. Any mixing of motives both fails to serve the best interests of patients and can only undermine trust on the part of the public and society in health care and the health professions. To prevent even the perception of questionable motivations, firewalls have been erected through policies and guidance from the United Network for Organ Sharing (UNOS) and Organ Procurement and Transplant network (OPTN) (see Chapter 4) to ensure that the health care teams caring for living patients cannot and must not be involved in the procurement of organs after a patient has died. Such separation of the care teams and procurement teams goes a long way toward ensuring patients and the public that the medical care they receive will not be influenced by the status as organ donors.

Even with rules in place, we know that certain groups-particularly African Americans-continue to worry that they will receive different care (meaning less aggressive) if they are known to be potential organ donors. These concerns persist despite concerted efforts on the part of organ procurement organizations (OPOs) and the transplant community at large to ensure the public that their care will not be compromised by their decision to donate organs after they die. It is easier to understand the legacies of mistrust when one considers the past treatment of African Americans at the hands of the majority population in the United States, including a checkered past when it came to medical research as well as access to clinical care.

A second major ethical issue in obtaining organs from deceased donors is the use of various definitions of death in the context of organ donation. From the beginnings of transplantation, deceased donation has lived by the so-called dead donor rule. As its name suggests, the dead donor rule requires that the donor be dead before his or her organs are removed. Because organs for transplantation must continue to be perfused up to or close to the time of their removal, traditional definitions of death involving the cessation of respiration and circulation, or whole-body death, may render organs unusable. These two requirements pose an obvious conflict, which required new definitions of death to be agreed on and applied in order for transplantation from deceased donors to occur.

The need to resolve this conflict prompted a focus on brain-based definitions of death, which allow for death to be declared based on the cessation of certain brain functions as measured by objective criteria (see Chapter 4). Thus, a patient could be declared dead even though circulation could be continued by the use of mechanical ventilation. Death by brain criteria, or so-called brain death, has been adopted in every state in the United States and in many countries around the world, so that death can be declared by either whole-body or brain criteria. Death by brain criteria is applied in situations outside of organ donation, of course, but its importance in deceased donation is clear.

Even though it has been widely adopted in medicine and law, death by brain criteria remains controversial. Because it relies to a great extent on criteria adopted by the medical community, it is a created standard unlike the more objective criteria of

whole-body death. In addition, because it is a socially constructed definition of death, the brain criteria standard sometimes comes under challenge on the grounds that as we learn more about brain physiology and function, the lines are less clear for determining when irreversibility of specific brain function occurs. Given the importance of the dead donor rule, it is critical that there be clarity about when death occurs. Just as some members of the public are concerned they will not receive adequate medical care if they are known to be organ donors, there is concern and misunderstanding that cuts across all groups about the criteria applied for pronouncing death in the context of organ donation.

Even with something like a consensus approach to brain-based definitions of death, there are remaining ethical issues in deceased donation, centering on the decision to donate. Ethically, the decision to donate must be fully voluntary and preferably made by the individual himself or herself; this is known as *first-person consent* and is usually indicated by some form of advance directive. This can include notation on a driver's license-now recognized by nearly half the states in the United States. If no such first-person consent is possible, consent of the family is sought. Concerns arise when family members are not in agreement about an individual's decision to donate, or when members of families do not agree with each other. These disagreements

---

often become the domain of OPO staff and hospital ethics committees, who do their best to resolve conflicts without resorting to the legal standing of advance directives.

Other Approaches to Determination of Death

The ongoing and chronic shortage of available organs has led to attempts to expand the eligibility of deceased donors. These efforts have focused on ways that would allow patients who are clearly at the end of life to become donors even though they will not “qualify” by applying death by brain criteria standards. Such approaches look to more traditional definitions of death involving the absence of circulatory function. Termed *donation after cardiac death* (DCD), these approaches attempt to adopt whole body death criteria while maintaining the perfusion necessary for transplantable organs (see Chapter 4). This requires creating an agreed-on limited time period during which cessation of circulation can be documented, but not so long as to deny the organs necessary perfusion. This problem has been addressed by consensus and consultation efforts involving a wide range of experts and stakeholders, including experts in the relevant medical subspecialties, bioethics and law, the transplant community, and the public.

In addition, a panel of the Institute of Medicine, appointed to address the question, issued a report and recommendations identifying guidelines under which DCD could be undertaken in ways that are both medically and ethically acceptable. The panel recommended critical care guidelines for DCD as well as identifying a time window of no less than 2 minutes and no longer than 5 minutes without spontaneous circulatory

function. Hospitals then create processes for their local use that rely on these guidelines, and there are increasing numbers of organs obtained from DCD donors.

Ethical Issues in the Distribution of Deceased Donor Organs

When organs become available from deceased donors, another set of issues arises in how they should be allocated. The ethical issues in the allocation of extremely scarce and life-saving resources is not restricted to kidneys or other solid organs, but it is an area in which the issues are acute and seemingly unrelenting. The system of oversight and regulations for the allocation of solid organs (through UNOS and OPTN) works to balance the often-competing goals of utility and fairness (see Chapter 4). On one hand, there is, and should be, a strong commitment to making the best use (utility) of the organs available for transplant. An emphasis on maximizing the utility of transplanted organs would favor allocation decisions that lead to the most possible years of healthy life in the recipient. This would disadvantage the older, sicker, less responsible, and so on.

Balanced against calculations of utility are questions of fairness-an approach that creates equality or equity of access and a sense that the system allocates organs in ways that are objective, transparent, and understandable and does not discriminate against particular individuals or groups. In practice, allocation of kidneys has more heavily favored fairness than utility, with a focus on length of time on waiting lists rather than limits based on age, health status, or other recipient-specific factors. One additional feature of the allocation of deceased donor organs is related to the existing system of a national network of OPOs.

Because the network exists to focus on organ recovery within geographic regions, there are important ethical issues regarding whether organs donated (and recovered) within a particular OPO region ought to be used within that region. It was easier to defend a local-first approach when the shipment of organs after procurement faced significant technical obstacles.

With the ability to transplant organs after longer cold ischemic times, however, and the development of a transportation infrastructure that can move shipments over great distances relatively quickly, it is difficult to defend on technical grounds a priority on local use first. The ethical issues become a question of which “community” owns or has first priority on use of organs, with community in this case defined by default as OPO region. Arguments from fairness support moving towards a national rather than a regional list. Kidney allocation continues to follow a regional prioritization because of the large numbers of recipients waiting for donated kidneys within every region, along with research that reduced cold ischemic time leads to better transplant outcomes.

ETHICAL ISSUES IN LIVING DONATION

Despite concerted efforts over many years to increase the supply of organs from deceased donors, the demand for transplantable organs continues to outstrip the available supply. To attempt to bridge this gap between supply and demand for organs, both transplantation centers and patients are turning to living donors as a source. This trend is evidenced by the fact that starting in 2003, most transplanted kidneys have come from living donors, although as of 2009, more donors are from the deceased.

Donations from living donors has, until recently, been associated with fewer rules and very limited oversight, owing to a combination of a different policy history and the practical realities of living versus deceased donation. First and most importantly, living donors have control over what happens to their bodies just as they do in any decisions about medical care. Respect for individual decision making is rooted in the principle of self-determination or autonomy and is realized in practice through the process of informed consent. Informed consent is primarily focused on the decision about whether to undergo the procedure to donate an organ but has also been viewed as including the decision about to whom the organ will be donated. This notion of “directed donation” has been the primary approach to living donation. In contrast to deceased donation, in which organs are viewed as the society's resource to allocate, in living donation the identification of the organ recipient is most often an integral part of the decision to donate. This is in sharp contrast to the approach taken to the allocation of deceased donor organs, in which donation and allocation are separated. The reliance on living donors to direct the donation of their organ raises numerous ethical issues, however.

The ethical issues surrounding living donation fall into three categories: (1) issues related to voluntary decision making, (2) issues related to payments or other incentives to donate, and (3) issues related to the selection of the recipient of donated organs-the allocation of living donor organs. First and foremost are lingering concerns regarding the quality of the decision by living donors to donate an organ. There are numerous anecdotes relating reports of family members feeling forced into donating a kidney or other organ, and there is a growing body of research attempting to assess the quality of informed consent among donors. Both focus on whether donors felt pressured to donate in ways that would undermine standards of ethically acceptable informed consent.

Second, given that prospective living donors and their recipients nearly always find each other on their own and then come to the transplantation center to be worked up, there are real concerns about promises or agreements made

---

that would be in violation of the National Organ Transplant Act (NOTA)[1]. This problem has been made much more real with the growth of living unrelated donation, which has been aided by the ability of prospective donors and recipients to connect much more easily through the Internet. Discussion and support forums allow individuals to make connections, as do the growing numbers of commercial websites like matchingdonors.com created expressly to facilitate (for a membership fee for the recipients) the matching of willing donors and waiting recipients. Although sites post statements about the illegality of payments, gifts, or other “valuable consideration,” it

is nearly impossible to enforce and so is left to transplantation centers to confront when patients arrive with willing donors who they met through these mechanisms.

Finally, and on a related point, unrelated living donation raises issues of how organs are allocated. Although related donors have an obvious connection to their recipient, the same cannot be said for living unrelated (or stranger) donors. Why should such unrelated donor organs go to a recipient who happens to be picked from a website rather than allocating the organ in the same way as deceased donor organs? These sorts of issues are important policy questions that will need to be faced as living donation continues to grow.

LOOKING FORWARD: THE FUTURE OF ETHICAL ISSUES IN TRANSPLANTATION

Xenotransplantation

There continue to be efforts to expand the pool of transplantable organs. During the past few decades, researchers have worked to genetically manipulate animals as a potential source for transplantable organs. These efforts are starting to realize some success, with breeding of populations of swine in carefully maintained facilities to ensure they are pathogen free. If animal sources for transplant prove successful, so-called xenotransplants could change the face of organ transplantation by effectively alleviating the existing shortage of human organs. There are, however, ethical issues with animal-to-human transplantation, including concerns about transmission of animal pathogens to humans, with subsequent human-to-human infection. In addition, there are always concerns raised by the use of animals for human benefit. These concerns focus on biomedical research uses, but xenotransplantation raises similar issues regarding animal rights, animal welfare, and human uses.

Paying for Organs

As the shortage of organs remains an ongoing and increasing challenge, discussion continues about issues of paying for organs. The debates about payment are not new; they have been around since the beginning of transplantation. In fact, some attribute the passage of NOTA in part to reactions to reported efforts to broker the sale of organs by an entrepreneurial physician of the 1980s. The arguments around payment tend to fall into two categories. Those that defend some sort of payment for organs base their position on the fact of extreme ongoing worldwide shortages or organs coupled with the rights of individuals to control what should happen to their bodies, including selling solid organs. The latter is a classic appeal to the importance of the ethical principle of respect for autonomy and all that goes with it. These arguments dismiss as paternalistic any claims that the medical profession or society ought to have a role in limiting whether individuals wish to donate, sell, barter, or otherwise distribute their organs.

In the few countries in the world in which there are gray or legal markets for organs, it appears that without stringent government regulation, the prospective sellers (rather than donors) are ripe for exploitation and sell their organs (almost always kidneys) out of desperation and a desire for a better life. Defenders of allowing the sale of organs point to Iran's approach as a more workable model, in which the government sets the price and conditions for the sale of organs, and then treats them as a resource to be allocated through the transplantation system. In the so-called “Iranian Model” uncontrolled direct payments by the recipients to the donors have become normative. Both the economic and psychosocial outcome of the Iranian donors has been poor and the Iranian authorities are having second thoughts about the wisdom of their “model”.

There have been some attempts to defend a true market in organs, in which an equivalent of eBay would be created to allow sellers to auction off their kidney to the highest bidder. Even carefully controlled efforts to increase the supply of organs through payments to sellers would require an exemption or change in NOTA, and proponents have called for pilot projects to assess how such programs would work as well as their effects on the transplantation system, the donation of organs through traditional means, and public perception of transplantation. Others have warned of the dangerous implications of such pilot projects.

In the meantime, there is a (grey-market) business in so-called transplant tourism, in which patients with means, usually from developed countries, travel to less developed countries to buy an organ from either a deceased or living donor. This has been met with much outcry over the exploitation of the poor and the vulnerable, questionable treatment of donors and recipients, and concern over the source of deceased donor organs (focusing on the use of executed prisoners in China). Recipients of these organs have been reported to suffer a high rate of complications, particularly infectious complication. In mid-2008, the transplant community responded with a detailed statement condemning transplant tourism and trafficking and proposing ethically acceptable alternatives (see the Appendix, “Declaration of Istanbul”).

Other Approaches

Since the beginning of the era of organ transplantation, there has been discussion about changing the way we deal with organs from deceased donors. Rather than allowing individuals and their families to decide whether to opt-in to organ donation after death, there have been numerous proposals that would

---

reverse the presumption and assume that individuals will be organ donors unless they opt-out. Versions of “presumed consent” have been tried in some European countries with limited success, and there are ethical and policy arguments against doing so in the United States. Chief among them is the sense that American society is heavily invested in individual choice, which flies in the face of presumed consent.

As outlined earlier in this chapter, public perception of transplantation is such that

presumed consent would not be easily welcomed. For this reason, discussions have not advanced past scholarly articles on a related approach, the outright expropriation of organs from individuals after they die.

CONCLUSION

The ongoing shortage of organs for transplantation encourages increasingly novel approaches to obtain more organs. It is clear that the organ transplant community will always need to include discussion of ethical and policy issues among the concerns that it faces in its attempt to save lives and improve the quality of life of patients with end-stage organ failure.

Selected Readings

Childress JF. Ethical criteria for procuring and distributing organs for transplantation. J Health Politics, Policy and Law 1989;14:87-113.

Childress JF. Ethics and the allocation of organs for transplantation. Kennedy Institute of Ethics Journal 1986;6:397-401.

Crowley-Matoka M, Arnold RM. The dead donor rule: how much does the public care … and how much should we care? Kennedy Institute of Ethics Journal 2004;14:319-332.

Danovitch GM. From Helsinki to Istanbul: what can the transplant community learn from experience in clinical research? Nephrol Dial Transplant 2008;23:1089-1092.

Danovitch G, Delmonico F. The prohibition of kidney sales and organ markets should remain. Curr Opin Organ Transplant 2008;13:386-394.

Gill J, Madhira B, Gjertson D, et al. Transplant tourism in the United States: a singlecenter experience. Clin J Am Soc Nephrol 2008;3:1820-1828.

Matas A, Hippen B, Satel S. In defense of a regulated system of compensation for living donation. Curr Opin Organ Transplant 2008;13:279-285.

Minniefield WJ, Yang J, Muti P. Differences in attitudes toward organ donation among African Americans and whites in the United States. J Natl Med Assoc 2001;93:372-379.

Shapiro, RS. Legal issues in payment of living donors for solid organs. Curr Opin

Organ Transplant 2002;7:375-379.

Siminoff LA, Sturm CM. African-American reluctance to donate: beliefs and attitudes about organ donation and implications for policy. Kennedy Institute of Ethics Journal 2000;10:59-74.

Truog RD, Miller FG. The dead donor rule and organ transplantation. N Engl J Med 2008;359:674-675.

Valapour M, Kahn JP, Rogers TB, et al. Living donors: what do they understand? Am J Transplant 2007;7(Suppl 2):283.

Washington H. Medical apartheid. New York: Random House, 2007.

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

19

Nutrition in the Kidney Transplant Recipient

Susan Weil

The nutritional management of the renal transplant recipient is an important determinant of outcome in terms of both morbidity and mortality. Diet can be used to prevent and ameliorate many transplant-related complications, although the precise nutrient requirements of kidney transplant recipients continue to be incompletely defined. The following recommendations provide a guide to nutrition care management in the pretransplantation, acute post-transplantation, and long-term post-transplantation periods.

PRETRANSPLANTATION NUTRITION MANAGEMENT

Major Concerns

In the pretransplantation period, a multidisciplinary approach should incorporate diet and lifestyle changes to help correct or improve malnutrition, dyslipidemia, obesity, renal osteodystrophy, and hypertension. To varying degrees, the presence of these comorbidities in the pretransplantation recipient is a predictor of related complications in the post-transplantation period. Although the etiology of these problems is multifactorial, it is reasonable to assume that appropriately aggressive nutritional management in the pretransplantation period may help minimize post-transplantation morbid events.

Malnutrition

The primary nutritional focus of the pretransplantation period is the prevention and treatment of malnutrition, some element of which has been identified in up to 70% of the dialysis population, in whom a low serum albumin level is a powerful predictor of mortality risk and morbidity. In data from the Centers for Medicare and Medicaid Services (CMS) 2006 Clinical Performance Measures Project, only 33% of adult hemodialysis and 19% of adult peritoneal dialysis recipients in the United States had albumin levels equal to or greater than 4 g/dL. Inadequate dialysis can compound the effect of malnutrition. In addition, chronic inflammation may cause low albumin,

malnutrition, and progressive atherosclerotic cardiovascular disease in dialysis recipients. The causes of inflammation are multifactorial, but proinflammatory cytokines such as inter-leukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) may play a central role. Markers of inflammation, such as C-reactive protein, are elevated in both peritoneal and hemodialysis patients, and inflammation appears to be a cause of hypoalbuminemia through increased albumin catabolism.

It is not entirely clear how these findings before transplantation may affect transplant outcome. Low serum albumin levels and other evidence of poor protein status are predictors of surgical risk and risk for infection. Aggressive treatment of malnutrition with oral supplements, tube feeding, or parenteral nutrition, as well as careful attention to dialysis adequacy and intervening causes of poor intake, not only may ultimately improve transplant outcome but also may allow transplantation to be an option for recipients who may otherwise have been excluded.

Obesity, Dyslipidemia, and Cardiovascular Disease

The incidence of postoperative wound complications, delayed graft function, and decreased recipient and graft survival may be increased in recipients with pretransplantation obesity. Morbidly obese patients (body mass index [BMI] ≥35 kg/m^2), have an increased risk for delayed graft function, prolonged hospitalization, acute rejection, and decreased overall graft survival compared with normal weight recipients (BMI 18.5 to 24.9 kg/m^2).

A BMI of greater than 30 kg/m^2 has also been associated with increased patient death and graft failure. Post-transplantation dyslipidemia, hypertension, and glucose intolerance have been observed in obese recipients and play a role in the development of cardiovascular disease. It has been suggested that obese recipients, particularly those with a coronary heart disease, should not undergo transplantation until weight loss has been achieved. However, it has not been established that a decrease in BMI while awaiting a transplant protects against graft loss or post-transplantation mortality.

Chronic kidney disease (CKD) stage V is associated with dyslipidemia, as evidenced by moderate hypertriglyceridemia with a normal total cholesterol; normal or increased triglyceride-rich low-density lipoprotein (LDL); decreased highdensity lipoprotein (HDL); increased cholesterol-rich very-low-density lipoprotein (VLDL); and increased susceptibility of LDL to oxidation. Decreased levels of apoprotein A-I and increased apoprotein B, apoprotein C-III, and lipoprotein(a) have also been described and contribute to the increased incidence of cardiovascular disease in this population. Attention to dialysis adequacy, treatment of anemia, dyslipidemia, secondary hyperparathyroidism, hypertension, diabetes, and possibly weight management in the transplant candidate can potentially improve outcomes. Decisions about transplantation suitability should be made on an individual basis taking numerous factors, including these, into consideration.

Renal Osteodystrophy

Abnormalities of mineral metabolism (elevated serum phosphorus, calcium, and calcium-phosphorus product), as well as secondary hyperparathyroidism, have been implicated in the etiology of nonatherogenic, medial calcification and cardiovascular disease in the CKD population. Abnormal bone and mineral metabolism and elevated parathyroid hormone levels have also been associated with increased risk for mortality in this population. Because these problems can persist and complicate the post-transplantation course (see Chapter 10), attempts should be made to control or correct them before transplantation.

Nutritional Assessment of the Transplant Candidate

Nutritional assessment of the transplant candidate should include the following:

- History—medical and dialysis history including comorbidities; current intake; gastrointestinal and appetite symptoms; use of medications, including vitamins and herbal preparations; physical activity and limitations; psychosocial and financial impediments to adherence to diet therapy; and allergies or food intolerance
- Physical and anthropometric assessment—height; weight; weight changes; evidence of muscle wasting and depletion of subcutaneous fat stores determined by subjective global assessment or other measurements; and physical evidence of vitamin deficiencies (triceps skin fold, arm muscle circumference, and midarm circumference may be unreliable as a consequence of variations in fluid status)
- Laboratory data—serum albumin and other plasma proteins such as prealbumin; lipid profile; anemia profile including hemoglobin, ferritin, transferrin saturation; bone disease profile including parathyroid hormone, phosphorus, and calcium; markers of dialysis adequacy (Kt/V); glycosylated hemoglobin (HgbAlc) in diabetics.

ACUTE POST-TRANSPLANTATION NUTRITION MANAGEMENT

Major Concerns

Protein Catabolism

The acute post-transplantation period generally refers to the 4- to 6-week period after surgery when the stress of surgery combined with the use of corticosteroids can lead to severe protein catabolism, particularly in recipients with underlying malnutrition. The primary goal is to provide adequate protein and calories to counteract protein

catabolism, promote wound healing, and decrease susceptibility to infection associated with protein malnutrition. Fortunately, modern immunosuppressive protocols have dramatically reduced the dose of corticosteroids typically employed in the postoperative period.

Fluid and Electrolyte Balance

During the postoperative period, fluid and electrolyte requirements vary depending on the level of renal function, volume status, and drug-nutrient interactions. Needs are assessed on an ongoing basis to balance between adequate hydration and volume overload. Specific guidelines are discussed under "Acute Post-transplantation Nutrient Requirements."

Drug-Nutrient Interactions

Drug-nutrient interactions, important in the long-term management of the transplant recipient, should also be considered in the acute postsurgical period. Table 19.1 lists both short- and long-term side effects, including nutrient interactions, of immunosuppressive agents. A special concern is the interaction between grapefruit and immunosuppressive agents. Grapefruit or grapefruit juice contains furanocoumarins, which inhibit the metabolic activities of cytochrome P-450 CYP3A4 isoenzyme, the most abundant P-450 enzyme, which is found primarily in liver and intestinal epithelial tissues. Levels of cyclosporine, tacrolimus, and sirolimus increase when taken concomitantly with grapefruit. Additional drug-nutrient interactions are discussed under "Long-Term Nutrition Management."

Acute Post-transplantation Nutrient Requirements

In the following sections, the recommendations listed as "per kilogram of body weight" should be based on actual body weight in the underweight or appropriate-weight patient, and possibly body weight adjusted for obesity in the obese patient, although evidence of the efficacy of such a correction is equivocal.

Protein

In the acute postoperative period, protein requirements are generally accepted to be 1.3 to 2 g/kg body weight. These levels are compatible with neutral or positive nitrogen balance, provided caloric intake is adequate. For recipients who continue to require dialysis, these levels of protein intake do not result in an increased dialysis requirement and therefore are used in patients with a functioning or nonfunctioning graft. With evidence of protein depletion, protein is provided at the upper end of the recommended range.

Calories

For the uncomplicated recipient, caloric requirements are 30 to 35 kcal/kg or 1.3 to 1.5 × basal energy expenditure (BEE) as determined by the Harris-Benedict equation, although this equation has not been systematically studied in kidney transplant recipients. This calorie level appears to be compatible with maintaining or achieving neutral or positive nitrogen balance.

TABLE 19.1 Side Effects of Immunosuppressive Agents

Agent	Side Effect
Corticosteroids	Polyphagia, glucose intolerance, hyperlipidemia, osteoporosis, gastritis and peptic ulcer disease, fluid retention, hypertension, protein catabolism, altered mood
Cyclosporin	Nephrotoxicity, neurotoxicity, hypertension, glucose intolerance, hyperlipidemia, hyperkalemia, hypomagnesemia, hyperuricemia, gingival hypertrophy
Azathioprine	Leukopenia, thrombocytopenia, megaloblastic anemia, nausea and vomiting, hepatic dysfunction
Atgam and Thymoglobulin	Chills, fever, leukopenia, thrombocytopenia, hyperglycemia (rare), diarrhea, nausea, vomiting
OKT3	Chills, fever, arthralgias, hypertension, pulmonary edema, nephrotoxicity, headache, encephalopathy, nausea, vomiting, diarrhea

Tacrolimus	Anemia, leukocytosis, hypertension, hyperglycemia, hyperkalemia or hypokalemia, hyperuricemia, hypomagnesemia, nausea, abdominal pain, gas, vomiting, anorexia, constipation, diarrhea, leukopenia
Mycophenolate mofetil (MMF)	Anorexia, nausea, epigastric pain, gas, diarrhea, abdominal pain
Sirolimus	Hypertriglyceridemia, hypercholesterolemia, thrombocytopenia, leukopenia, hypokalemia, delayed wound healing (at high doses); diabetogenic
Basiliximab and daclizumab	Vomiting

Carbohydrates

About 50% to 60% of calories should be from carbohydrate sources, with diet modifications as needed in the presence of diabetes. Several small, early studies demonstrated that limitation of carbohydrates in combination with a high protein diet minimized cushingoid facies in renal transplant recipients; however, these studies have not been repeated in a larger population or on a long-term basis.

Fat

Diet modification for dyslipidemia, a key issue in the long-term management of transplant recipients, can be introduced in the early postoperative period, assuming calorie requirements are easily met. Up to 35% of calories from fat can be provided, in keeping with the National Heart, Lung, and Blood Institute Adult Treatment Panel III Guidelines and adapted by the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (Table 19.2).

Sodium

Hypertension and volume overload are common in the post-transplantation period. Calcineurin inhibitor-related hypertension is partly salt dependent. In these circumstances, control of sodium intake to 2 g per day is appropriate. Normotensive recipients who are edema free do not require strict sodium restriction.

TABLE 19.2 Therapeutic Lifestyle Changes for Adults with Chronic Kidney Disease

Diet*
Emphasize reduced saturated fat:
Saturated fat: <7% of total calories
Polyunsaturated fat: up to 10% of total calories
Monounsaturated fat: up to 20% of total calories
Total fat: 25% to 35% of total calories
Cholesterol: <200 mg per day

Carbohydrate: 50% to 60% of total calories

Emphasize components that reduce dyslipidemia

Fiber: 20 to 30 g per day; emphasize 5 to 10 g per day viscous (soluble) fiber

Consider plant stanols/sterols 2 g per day

Improve glycemic control

Emphasize total calories to attain/maintain standard NHANES body weight

Match intake of overall energy (calories) to overall energy needs

Body mass index 25 to 28 kg/m^2

Waist circumference

Men <40 inches (102 cm)

Women <35 inches (88 cm)

Waist-to-hip ratio (men <1; women <8)

Physical Activity

Moderate daily lifestyle activities

Use pedometer to attain/maintain 10,000 steps per day

Emphasize regular daily motion and distance (within ability)

Moderate planned physical activity

Three to 4 times per week, 20- to 30-minute periods of activity

Include 5-minute warm-up and cool-down

Choose walking, swimming, supervised exercise (within ability)

Include resistance exercise training

Emphasize lean muscle mass and reducing excess body fat

Habits
Alchohol in moderation: limit one drink per day with approval of physician
Smoking cessation

* Consult a dietitian with expertise in chronic kidney disease.

NHANES, National Health and Nutrition Examination Survey.

From the National Kidney Foundation. KDOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease. Am J Kidney Dis 2003;41(Suppl 3):S1-S92, with permission.

Potassium

Hyperkalemia, often seen in the post-transplantation period in the presence of the calcineurin inhibitors or impaired graft function, may be exaggerated with the use of β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, acidosis, and potassium-containing phosphorus supplements. Treatment of hyperkalemia may require dietary potassium restriction or more aggressive measures. If potassium restriction is warranted, about 1 mEq of potassium should be allowed per gram of protein in the diet, so as not to interfere with adequate protein intake.

Phosphorus

Hypophosphatemia is a common finding after transplantation, in part as a result of

persistent secondary hyperparathyroidism, although it can continue after parathyroid hormone (PTH) levels normalize. Fibroblast growth factor-23 (FGF-23), also known as *phosphotonin,* has been identified as a key cause of hypophosphatemia after transplantation. Phosphotonin induces phosphaturia, inhibits calcitriol synthesis, and accumulates in CKD independent of PTH levels. In addition, glucocorticoid-induced gluconeogenesis in the renal proximal tubule contributes to phosphaturia. Increased intake of high-phosphorus foods may not be sufficient for repletion, and oral replacement is often necessary.

In the presence of delayed graft function, the use of phosphate-binding antacids may be temporarily warranted to control hyperphosphatemia. An interaction has been identified between sevelamer hydrochloride and mycophenolic acid that results in lowered mycophenolic acid levels. so caution should be used when both medications are prescribed.

Magnesium

Hypomagnesemia, which may exacerbate calcineurin inhibitor-related neurotoxicity, is a common postoperative finding secondary to hypermagnesuria. Dietary replacement of magnesium is likely to be inadequate, and magnesium supplements are often prescribed, although their effectiveness is unproved in the presence of persistent urinary losses.

Fluid Intake

Early post-transplantation fluid management is discussed in Chapter 9. For a normovolemic recipient with a well-functioning graft, a reasonable minimum fluid intake is 2000 mL per day. For an oliguric recipient, a volume of fluid should be provided to equal urine output plus a minimum of 500 to 750 mL to cover insensible losses. Variations should be determined by volume status and blood pressure, typically erring on the positive side, as urine output increases.

Vitamins

Replacement of water-soluble vitamins containing B complex and up to 100 mg of vitamin C should be continued if post-transplantation dialysis is required. High doses of vitamin C should be avoided both in the pretransplantation and post-transplantation periods to minimize risk for secondary oxalosis and potential oxalate deposition in the transplanted kidney (see “Nutrient Recommendations for the Stable Transplant Recipient”).

Trace Minerals

Iron. Iron deficiency, defined as a transferrin saturation (iron and total ironbinding

capacity) of less than 20% or a serum ferritin level of less than 100 ng/mL, is a common finding in CKD patients receiving erythropoietin, particularly those not treated with hemodialysis, when intravenous iron is typically provided. A preoperative evaluation of iron status and correction of deficiency is indicated to optimize the prevention and treatment of anemia. Hematocrit values of greater than 30% may reduce cardiovascular events in the early postoperative period. Iron deficiency itself has been independently associated with post-transplantation cardiovascular events, beyond anemia alone.

Other Trace Minerals. Post-transplantation trace mineral requirements have not been well investigated. Zincuria is associated with steroid therapy, although its clinical significance is not well substantiated. Low selenium levels, a contributing factor to oxidative stress, have also been identified in some transplant recipients. Evidence suggests that levels return to normal after transplantation with improvement in oxidative stress parameters; however, this area warrants further investigation. Routine supplementation of trace minerals is not indicated in recipients on an oral diet.

NUTRITIONAL SUPPORT IN THE POST-TRANSPLANTATION PERIOD

In nutritionally high-risk recipients, early nutritional support is indicated. Use of aggressive nutritional support in recipients with CKD and septic complications, including transplant recipients, reduces mortality rates.

In the typical post-transplantation course, progression to solid foods occurs within 2 to 3 postoperative days. The length of hospitalization may be less than 5 days, and aggressive nutritional support is rarely necessary. The following guidelines, however, can be used for transplant recipients, who may not be able to tolerate oral nutrition for prolonged periods. This problem is more commonly seen in combined kidney-pancreas transplant recipients.

Indications for Aggressive Nutritional Intervention

Delayed or Inadequate Oral Intake

Parenteral nutrition may be warranted if postoperative oral intake is delayed for more than 5 days. The decision to begin parenteral nutrition should be made only after failed attempts at oral intake and tube feeding, or if either route is contraindicated. Any patient unable to sustain adequate intake to meet protein and calorie needs after the fifth postoperative day is considered a potential candidate for some type of nutritional intervention, depending on the nutritional status of the recipient, degree of catabolism, and amount of intake deficit.

Choice of Feeding Modality

Oral Supplements

Supplements are considered 4 to 5 days after surgery in any recipient in whom protein and calorie needs are not being met on a standard diet. Correctable causes for inadequate oral intake should be assessed, such as overly restrictive diet, unnecessarily slow progression to a full diet, and interference with meals by dialysis, scheduled tests, and procedures.

Tube Feeding

Tube feeding, rarely required after kidney transplantation, is considered in the postoperative period in any recipient with a functional gastrointestinal tract

who, by postoperative day 5, is unable to maintain adequate protein and calorie nutrition by diet or oral supplements. Small bowel access and use of continuous feeding are preferred when tube feeding is indicated. Tube feeding is preferred over parenteral nutrition because of a decreased risk for infection related to central line use, to help maintain normal intestinal function and integrity, and to prevent intestinal bacterial overgrowth. A wide variety of high nitrogen oral and enteral products are commercially available.

Total Parenteral Nutrition

A mixture of both essential and nonessential amino acids, fat, and dextrose should provide a daily intake of at least 1.5 g protein/kg and 30 to 35 kcal/kg.

Dietary Considerations During Acute Rejection Episodes

During acute rejection episodes, provision of optimal protein and calorie intake is the primary nutritional concern. High-dose steroids produce a dose-related increase in protein catabolic rate, leading to severe catabolism. Protein intake providing at least 1.5 g/kg is appropriate.

LONG-TERM NUTRITION MANAGEMENT

A successful kidney transplantation represents a long-awaited opportunity to be liberated from previous diet restrictions. When providing diet instruction, this need for “liberation” should be recognized and directed in a manner that will permit the recipient a well-deserved sense of freedom without potentially morbid dietary indiscretion. In the presence of varying degrees of chronic allograft nephropathy, nutrition guidelines should be implemented in keeping with KDOQI recommendations for CKD stages I to IV, with adjustments as appropriate considering the use of immunosuppressive agents and other comorbidities.

Major Concerns

Dyslipidemia

Cardiovascular disease remains the main cause of long-term mortality in the transplant population. Risk factors for cardiovascular disease in the transplant population are thought to include dyslipidemia, diabetes mellitus, hypertension, male sex, advanced patient age, and cigarette smoking. Other possible risk factors include hyperhomocysteinemia, elevated C-reactive protein, elevated lipoprotein(a), obesity, and allograft loss rejection. Post-transplantation dyslipidemia occurs in up to 80% to 90% of transplant recipients and is associated with use of corticosteroids, cyclosporine, and sirolimus and potentially aggravated by obesity as well as diabetes, excessive alcohol intake, chronic liver disease, hypothyroidism, and nephrotic syndrome. In addition to the development of cardiovascular disease, chronic allograft nephropathy may be enhanced by hyperlipidemia.

Transplant recipients treated with cyclosporine may have elevated total and LDL cholesterol levels as a result of a direct effect on cell membrane cholesterol concentration and regulatory pools, resulting in both increased synthesis of cholesterol and decreased clearance of LDL. HDL levels are typically reduced. As part of the "metabolic syndrome," elevations of non-HDL cholesterol, including LDL, lipoprotein(a), intermediate-density lipoprotein, and VLDL, may also be present. The hyperlipidemic effect of corticosteroids is well established and is thought to result from increased hepatic VLDL synthesis, down-regulation of LDL receptors, and perhaps adrenocorticotropic hormone suppression. Sirolimus is associated with hypertriglyceridemia in part due to blockage of insulin-stimulated lipoprotein lipase. Because of the high incidence of atherosclerotic events in the population, transplant recipients should be

---

considered in the highest cardiovascular risk group. Goals for lipid lowering are based on the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) and KDOQI guidelines (see "Selected Readings"). Lifestyle modification, including diet and exercise, may be at least partially effective in lipid reduction after transplantation.

Homocysteine

Homocysteine is a nonessential amino acid that is formed from the essential amino acid methionine and is an intermediate in the synthesis of cysteine. Hyperhomocysteinemia has been identified as a risk factor for the development of cardiovascular disease (CVD) in the general population, an association also made with people with CKD, including transplant recipients. Low levels of pyridoxine, folic acid, vitamin B_{12}, and serum albumin; advancing age; renal impairment; and a genetic mutation in

methylenetetrahydrofolate reductase, which limits the conversion of homocysteine to methionine, correlate with homocysteine levels. The Folic Acid for Vascular Outcome Reduction In Transplantation (FAVORIT) trial is a large (4000 patients) multicenter, double-blind randomized controlled clinical trial designed to evaluate whether lowering homocysteine levels using vitamin supplementation (either a high-dose or low-dose of folic acid [5 or 10 mg], vitamin B_6 [50 or 1.4 mg], and vitamin B_{12} [1000 or 2 μg]) reduces CVD events in renal transplant recipients. The primary end point is a composite of incident or recurrent CVD outcomes. The study will not be completed until 2010.

Obesity and Weight Gain

Hyperphagia associated with steroid therapy, together with a sense of liberation from the previous dietary constraints and an increased sense of well-being, contributes to the propensity for weight gain after transplantation. Obesity can contribute to the development or exacerbation of hypertension, dyslipidemia, cardiovascular disease, and diabetes mellitus.

The reported prevalence of post-transplantation obesity varies, although about 50% of recipients experience weight gain after transplantation. The average weight gain is 10% of body weight at 1 year. Demographic factors such as female gender, young age, and African American race are associated with the most weight gain in the first 2 years after transplantation.

Management of Obesity. In addition to limitation of caloric intake, management of post-transplantation obesity includes behavior modification, an exercise program, and early intensive nutritional counseling. Frequent follow-up by members of the health care team, including a physician, dietitian, and nurse, along with group support techniques, may optimize adherence to weight management programs. Medications used to treat obesity in the general population have not been well studied in the renal transplant population. Potential side effects of increased blood pressure are associated with sibutramine. Decreased cyclosporine bioavailability and interference with cyclosporine absorption have been reported with orlistat, a nonsystemic gastrointestinal lipase inhibitor. Orlistat, and the more recently available over-the-counter version Alli, carry a U.S. Food and Drug Administration (FDA) warning on the package insert to avoid if taking cyclosporine.

There is limited experience with gastric bypass surgery in morbidly obese transplant candidates and recipients. Preliminary reports suggest that this option is safe and effective, and it may well become more popular as experience broadens. Post-transplantation weight gain is consistently improved when steroid minimization immunosuppression protocols are used.

Bone Disease

Diet plays both a palliative and a preventive role in certain post-transplantation bone abnormalities. Osteoporosis has been associated with long-term glucocorticoid use in part as a result of decreased intestinal absorption of calcium and suppression of bone formation. Cyclosporine and tacrolimus may also contribute to bone loss, although the pathogenesis and association have not been fully investigated. Persistent hyperparathyroidism, even in the presence of good kidney function, occurs in up to 50% of transplant recipients and influences the severity of bone loss and contributes to persistent hypercalcemia and hypophosphatemia. Cinacalcet, a calcimetric agent that decreases secretion of PTH has been shown to be effective in lowering PTH and correcting hypercalcemia in this setting. Most of the bone loss after transplantation occurs in the first 6 months. Provision of adequate calcium, phosphorus, and vitamin D may attenuate these problems. The efficacy of active vitamin D analogues in transplant recipients with hyperparathyroidism has not been fully elucidated. Given the presence of poor vitamin D nutrition in patients with CKD, and the advice often given to transplant recipients regarding limiting sun exposure, it is appropriate to assess 25-hydroxyvitamin D nutrition in the transplant recipient and to supplement accordingly. Correction of metabolic acidosis also plays a key role in minimizing bone loss as well as in optimizing protein nutriture. Weight-bearing exercise is also beneficial for managing or preventing osteoporosis.

Hypertension

The prevalence of hypertension in transplant recipients is between 60% and 80%. Elevations in blood pressure and pulse pressure are important risk factors for cardiovascular disease and death as well as decreased graft survival in transplant recipients. Although post-transplantation hypertension is multifactorial in origin, calcineurin inhibitors are known to enhance sympathetic nervous system activity, renal vascular resistance, and sodium-water retention. Patients who are hypertensive and treated with calcineurin inhibitors are generally recommended to follow a sodium-controlled diet. Routine sodium restriction of all transplant recipients is not justified, and sodium intake recommendations should be individualized. Weight loss in the obese hypertensive recipient may also play an important role in lowering blood pressure, and exercise may also provide a beneficial adjuvant. Avoidance of alcohol for purposes of blood pressure control has not been evaluated in this population.

New-Onset Diabetes Mellitus After Transplantation

New-onset diabetes after transplantation (NODAT; see Chapter 10) occurs in roughly 25% of patients within the first 3 years after renal transplantation. Risk factors for development of diabetes include obesity, family history of diabetes, African or Hispanic ancestry, hepatitis C virus infection, increased recipient age (>40 years), calcineurin inhibitor use, and corticosteroid use. Male donor gender, HLA mismatch, and cause of underlying renal disease may also confer an increased risk. Transplant recipients who develop diabetes are at greater risk for graft-related complications, including graft

rejection, graft loss and infection, vascular complications, and the risk for complications of diabetes itself. The development of NODAT also confers an increased mortality risk. Referral to a dietitian for diet and weight loss counseling, exercise, and decreased dosing or withdrawal of corticosteroids, provide the basis for initial management. Oral hypoglycemic agents or insulin may be warranted.

Progression of Renal Disease in Kidney Transplants

It has not been determined whether diet has a role in the progression of renal disease in the transplanted kidney. Studies suggest that protein restriction may be helpful in the presence of chronic allograft nephropathy and may help to decrease the associated proteinuria. It is possible, based on data in patients with CKD, that those with diabetic nephropathy may be more responsive to a low protein diet than those with CKD of other etiologies. Protein status must be closely monitored to avoid malnutrition, as evidenced by hypoalbuminemia, a predictor of mortality in the transplant recipient. In addition to its possible role as a predictor of mortality, hypoalbuminemia is associated with decreased renal graft survival, increased risk for cytomegalovirus infection and other infections, and graft loss.

The optimal dose of protein remains to be determined, although 0.8 to 1.0 g protein/kg has been recommended. Evidence of continued protein wasting has been described even with low doses of corticosteroids, necessitating ongoing assessment of nutritional status for recipients on low-protein diets. It has been suggested that soy protein may confer an advantage over animal proteins.

The metabolic syndrome (MS) is typically defined as a collection of at least three metabolic risk factors. The root causes of metabolic syndrome are overweight or obesity, physical inactivity, and genetic factors. Various risk factors have been generally accepted as characteristic of this syndrome: abdominal obesity, atherogenic dyslipidemia (high triglycerides and low HDL cholesterol), hypertension, insulin resistance with or without glucose intolerance, prothrombotic state, and proinflammatory state. In transplant recipients, the presence of MS after transplantation has been shown to adversely affect both graft and patient survival, although early treatment interventions, including diet, may mitigate the impact of MS.

Foodborne Infectious Complications

Attention to potentially pathogenic organisms commonly found in food may provide a relatively simple preventive measure to avoid certain infections. Providing education on safe and sensible food habits may help to minimize the morbidity associated with certain post-transplantation infectious diseases.

Food vehicles for *Listeria monocytogenes* include raw milk, soft cheeses, and hot dogs. *Nocardia asteroides*, although ubiquitous in the environment and not uncommonly

nosocomially acquired, can be present in decaying vegetables. *Salmonella* species infections are associated with undercooked, contaminated meat, poultry, and eggs, as well as raw milk. The potential for *Legionella* species infection exists in areas with a contaminated or unsafe water supply. *Salmonella Kottbus, Salmonella enteritidis,* and *Escherichia coli* are associated with ingestion of raw sprouts, whereas *Salmonella* serotype *Poona* infections have resulted from imported cantaloupe. Anisakiasis, caused by human infection with *Anisakis larvae*, and *Vibrio cholerae 01* and *0139* are linked to eating raw or undercooked fish. Prevention includes proper food selection, handling, preparation, storage, and pasteurization, and careful selection when eating out.

Foodborne Noninfectious Complications

Transplant recipients with impaired renal function should be advised to avoid ingestion of star fruit (*Averrhoa carambola*). Although formerly a rare fruit typical to some Asian cuisines, it is now commonly available in grocery stores. Intake of star fruit in people with impaired renal function is associated with severe neurologic symptoms and death.

Use of Herbal Teas, Supplements, and Other Considerations

The use of herbal medicines and inclusion of herbal medicines in food items, such as juices, is increasingly common. In the United States, herbal medicines are regulated as food products and dietary supplements and are not tested for safety or efficacy by the FDA. These products pose a special potential risk for transplant recipients for several reasons. One concern is the lack of information about drug-nutrient interactions and whether these substances increase or decrease the effectiveness of immunosuppressants or other prescribed medications. One well-described example is the interaction between St. John's wort and cyclosporine. St. John's wort, a potent inducer of CYP3A4, enhances plasma clearance of a number of drugs, such as cyclosporine. Coadministration of cyclosporine and St. John's wort results in a rapid and significant reduction of plasma cyclosporine concentrations and alterations in cyclosporine metabolite kinetics that may affect the toxicity profile of the drug. A traditional English breakfast (Earl Grey tea and toast with bitter orange marmalade) may also modify cyclosporine metabolism. The flavanoid naringenin and the furanocoumarin bergamottin are potent inhibitors of one subset of CYP P-450 enzymes. These and other flavonoids are found in grapefruit but also have been described in bitter oranges (citrus aurantium), pomegranate, star fruit, and bergamot, which gives Earl Grey its distinct flavor. Quercitin, a flavonol, found in onions, red wine, green tea, and many other foods and supplements, is a potent inhibitor of CYP 3A4, so may also decrease cyclosporine bioavailability. Two other teas, orange peel and chamomile, are known to raise cyclosporine levels. Chamomile has been demonstrated to inhibit CYP P-450 enzymes *in vitro*. Red yeast rice (*Monascus purpureus*), an herbal preparation used to lower cholesterol, has induced rhabdomyolysis in stable renal transplant recipients. Rice fermented with red yeast contains mevinic acids, as does lovastatin, a coenzyme A

reductase inhibitor with known potential at higher doses for rhabdomyolysis, when taken with cyclosporine.

Another related concern is that certain herbs and food products, such as Echinacea, Astragalus, and Noni juice, appear to contain immune-enhancing properties. *In vitro* lymphocyte proliferation tests using phytohemagglutinin, mixed lymphocyte culture (MLC) assay, and IL-2 and IL-10 production from MLC, demonstrated that dong quai, ginseng, and milk thistle had nonspecific immunostimulatory effects on lymphocyte proliferation. Ginger and green tea have immunosuppressive effects. Dong quai and milk thistle increase all responsiveness in MLC, whereas ginger and green tea decrease these responses. The immunostimulatory effects of dong quai and milk thistle were consistently seen in both cell-mediated immune response and nonspecific lymphoproliferation. The immunosuppressive effect of green tea and ginger were mediated through a decrease in IL-2 production, but the immunostimulatory effects of dong quai and milk thistle were not. Green tea, dong quai, ginseng, milk thistle, and ginger have varying effects on *in vitro* immune assays that may be relevant in transplant recipients and should be avoided or used with caution.

Some herbal preparations have been found to contain heavy metals and toxic botanicals. Because there are no sanitation standards for herbal medicines, the potential for microbial contamination poses a particular risk for the immune-suppressed recipient. Although this area has been poorly studied and data are, in part, anecdotal, physicians, patients, and other health care professionals should be aware of this problem. Until and unless adequate research and appropriate regulations exist, herbal products and teas should be discouraged or closely monitored in transplant recipients.

Another consideration is the possible benefit of "immunonutrition." New transplant recipients who receive dietary supplementation with arginine and

---

omega-3 and omega-9 fatty acids (canola oil), may have a lower incidence of NODAT, post-30-day rejection rates, cardiac events and sepsis. Further studies will help determine the precise role of such supplementation.

Nutrient Recommendations for the Stable Transplant Recipient

Protein and Calories

Post-transplantation protein requirements for stable transplant recipients are not well defined, with muscle wasting identified even at corticosteroid doses of 0.20 mg/kg per day. A daily protein intake of 1.0 g/kg has been recommended for stable transplant recipients with normal renal function. Negative nitrogen balance has been reported in short-term studies of protein intake levels of 0.6 g/kg per day unless calorie intake is maintained above 25 kcal/kg per day. A daily protein intake approaching 1 g/kg,

combined with an adequate calorie intake, appears to be compatible with neutral or positive nitrogen balance. Lower levels may be appropriate for recipients with chronic allograft nephropathy, as discussed previously.

For stable transplant recipients who require weight reduction, a daily calorie intake of 25 kcal/kg ideal body weight is a reasonable starting point. Caloric restriction should be combined with exercise, behavior modification techniques, and regular follow-up.

Fat and Carbohydrate

Given the propensity toward weight gain, the incidence of post-transplantation dyslipidemia, and its potential contribution to decreased graft survival, a reduced fat and reduced cholesterol diet is appropriate for most transplant recipients. The recommendations of ATP III (see “Selected Readings”) incorporate a Therapeutic Lifestyle Change (TLC) program that includes diet. The KDOQI guidelines for management of dyslipidemias considers all CKD recipients to be in the high-risk category and advocates use of the TLC guidelines. Table 19.2 details the specific recommendations of these guidelines. For recipients who require pharmacologic management for control of hypercholesterolemia, diet guidelines should continue to be encouraged as adjunctive therapy. For transplant recipients with NODAT or preexisting diabetes mellitus, complex carbohydrates should be emphasized, with limitation of simple sugars as needed to control glucose levels. A high fiber intake (25 to 30 g per day) can assist with blood glucose and blood cholesterol control.

Fish Oil

There is insufficient evidence to recommend the routine use of fish oil to improve renal function, rejection rates, and patient or graft survival.

Sodium

Sodium restriction to 2 to 3 g per day is warranted in calcineurin inhibitortreated recipients with hypertension. In normotensive, nonedematous recipients, strict sodium restriction is not warranted.

Potassium

Hyperkalemia, associated with the use of cyclosporine and tacrolimus, may continue to be observed in otherwise stable transplant recipients. Guidelines, as discussed under “Acute Post-transplantation Nutrition Management” continue to apply in this setting. Potassium levels up to 5.5 mEq/L are common and are rarely a source of concern in stable recipients.

Calcium, Phosphorus, and Vitamin D

Calcium should be provided at the level of 1000 to 1500 mg per day by a combination of diet and supplements. Vitamin D, either 25-hydroxyvitamin D_2 or 1,25-dihydroxyvitamin D_3 (0.25 μg), should be supplemented, with dosing based on vitamin D levels. 1,25-Dihydroxyvitamin D_3 is generally instituted in recipients with a glomerular filtration rate (GFR) of less than 30 mL per minute. Whether routine use of calcidiol should be used as opposed to calcitriol at higher GFRs is under debate. Hypophosphatemia and hypercalcemia may persist, and although not entirely explained by PTH levels, residual hyperparathyroidism should be addressed. In chronic allograft nephropathy, hyperphosphatemia and other manifestations of renal osteodystrophy should be treated using guidelines for stage 3 and 4 CKD.

Magnesium

Hypomagnesemia may persist into the long-term post-transplantation period, and magnesium supplements are often prescribed. Serum magnesium has been reported to correlate negatively with an atherogenic lipid profile in individuals with diabetes mellitus and metabolic syndrome, although this correlation is not well defined in the transplant recipient. The role of magnesium in controlling blood pressure in this population remains equivocal.

Vitamins

The efficacy of routine supplementation of certain water-soluble vitamins, specifically pyridoxine, B_{12}, and folic acid, is under investigation (see “Homocysteine”). Specific requirements for other vitamins in kidney transplant recipients continue to be poorly defined. In cyclosporine-treated patients, antioxidant supplementation with vitamin E, vitamin C, and β-carotene has been reported to decrease cyclosporine levels. Caution should be used in prescribing vitamin supplements and when monitoring of patients who are taking supplements until precise needs are defined and interactions are elucidated.

Alcohol

Excessive alcohol intake may interfere with the metabolism of immunosuppressive agents, although moderate amounts may be well tolerated. An interaction has been identified specifically between cyclosporine and red wine, similar to that of grapefruit juice. Red wine inactivated CYP 3A4 at a rate about 16% that of grapefruit juice.

Heavy alcohol use is also associated with increased risk for avascular necrosis and bone loss as well as hypertension. Other medications prescribed to transplant recipients should be screened for drug and alcohol interactions.

Exercise

Physical training is a vital part of the management of the transplant recipient. Patients

tested before and shortly after renal transplantation show improvement in exercise capacity independent of improvement in anemia. Although renal transplant recipients are a relatively highly functioning group compared with the dialysis population as a whole, these individuals may have significant exercise deficits before transplantation. Potassium, magnesium, calcium, and phosphate abnormalities after transplantation may affect muscle function but have not been specifically studied in transplant recipients, as may adverse drug effects from the combination of statins and calcineurin inhibitors and steroid myopathy. Exercise can attenuate some of the side effects of immunosuppressive therapy, such as protein catabolism and muscle wasting, dyslipidemia, hypertension, osteoporosis, and obesity, along with improving glucose control

---

in diabetics and quality of life. Although the optimal exercise program is not defined in the transplantation population, recommendations for the general population, which include cardiovascular conditioning and muscle strengthening, are appropriate for most recipients with maximum benefit observed in previously sedentary patients who engage in even minimal activity. Renal transplant recipients should begin a walking program immediately following discharge from the hospital, averaging 30 minutes daily.

Nutrient Recommendations for the Pregnant Transplant Recipient

The protein needs of stable pregnant transplant recipients are 0.8 g/kg pregravida ideal or adjusted body weight plus 10 g per day. Caloric requirements can be calculated using basal energy expenditure times an activity factor of 1.2 to 1.4; an additional 300 kcal per day should be consumed in the second and third trimesters. Other nutrient requirements are the same as for nontransplanted pregnant women, although close monitoring is appropriate in terms of weight gain and glucose control because of the risk for glucose intolerance. Residual secondary hyperparathyroidism may also require adjustments in phosphorus, calcium, and vitamin D intake.

Selected Readings

Aalten J, Christiaans MH, de Fijter H, et al. The influence of obesity on short- and long-term graft and patient survival after renal transplantation. Transpl Int 2006;19:901-907.

Alexander JW, Metze TJ, McIntosh MJ, et al. The influence of immunomodulatory diet on transplant success and complications. Transplant 2005;79:460-465.

Alexander JW, Goodman H. Gastric bypass in chronic renal failure and renal transplant. Nutr Clin Pract 2007;22:16-21.

Bernardi A, Biasia F, Pati T, et al. Long-term protein intake control in kidney transplant recipients: effect in kidney graft function and in nutritional status. Am J Kidney Dis 2003;41(Suppl 1):S146-S152.

Blackhall ML, Fasset RG, Sharman JE, et al. Effects of antioxidant supplementation on blood cyclosporine A and glomerular filtration rate in renal transplant recipients. Nephrol Dial Transplant 2005;20:1970-1975.

Bostom AG, Carpenter MA, Kusek JW, et al. Rationale and design of the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial. Am Heart J 2006:152:448.E1-7.

Centers for Medicare & Medicaid Services. 2006 Annual Report, End Stage Renal Disease Clinical Performance Measures Project. Department of Health and Human Services, Centers for Medicare & Medicaid Services, Office of Clinical Standards & Quality, Baltimore, MD, January 2007.

Chertow GM, Goldstein-Fuchs DJ, Lazarus JM, Kaysen GA. Pre-albumin, mortality, and cause-specific hospitalization in hemodialysis patients. Kidney Int 2005;68:2794-2800.

Cupisti A, Ghiadon L, D'Allessandro C, et al. Soy protein diet improves endothelial dysfunction in renal transplant patients. Nephrol Dial Transplant 2007;22:229-234.

Gore JL, Pham PT, Danovitch GM, et al. Obesity and outcome following renal transplantation. Am J Transplant 2006;6:357-363.

Grundy SM, Cleeman JI, Merz CN, et al. National Heart, Lung and Blood Institute: American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227-239.

Guida B, Trio R, Laccetti R, et al. Role of dietary intervention on metabolic abnormalities and nutritional status after renal transplantation. Nephrol Dial Transplant 2007;22:3304-3310.

Hasse JM, Blue LS, eds. Comprehensive Guide to Transplant Nutrition, 1st ed. Chicago: American Dietetic Association, 2002.

Johansen KL. Exercise in the end-stage renal disease population. J Am Soc Nephrol 2007;18:1845-1854.

Kasiske B, Cosio FG, Beto J, et al. Clinical practice guidelines for Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant 2004;4(Suppl 7):13-53.

Leca N, Laftavi M, Gundroo A, et al. Early and severe hyperparathyroidism associated with hypercalcemia after renal transplant treated with cinacalcet. Am J Transplant 2006;6:2391-2395.

Lim AK, Manley KJ, Robert MA, Fraenkel MB. Fish oil treatment for kidney treatment for kidney transplant recipients: a meta-analysis of randomized controlled trials. Transplantation 2007;83:831-838.

Moreau K, Chauveau P, Martin S, et al. Long-term evolution of body composition after renal transplant: 5 year survey. J Ren Nutr 2006;16:291-299.

Nowak, R, Nowak, B. Herbal teas interfere with cyclosporine levels in renal transplant patients. Nephrol Dial Transplant 2005;20:2554-2556.

Painter P. Exercise following organ transplantation: a critical part of the routine post-transplant care. Ann Transplant 2005;10:28-30.

Ramesh Prasad GV, Huang M, Nash MM, Zaltzman JS. The role of dietary cations in the blood pressure of renal transplant recipients. Clin Transplant 2006;20:37-42.

Retkowski O, Wienke A, Hamza A, et al. Low body mass index in kidney transplant recipients: risk or advantage for long-term graft function? Transplant Proc 2007;39:1416-1420.

Roodnat JI, van Gurp EA, Mulder PG, et al. High pretransplant parathyroid hormone levels increase the risk for graft failure after renal transplantation. Transplantation 2006;82:362-367.

Sprague SM, Belozeroff V, Danese MD, et al. Abnormal bone and mineral metabolism in kidney transplant patients: a review. Am J Nephrol 2007;28:246-253.

Srinivas TR, Meier-Kriesche HU. Obesity and kidney transplantation. Contrib Nephrol 2006;151:19-41.

Wilasrusmee C, Siddiqui J, Bruch D, et al. *In vitro* immunomodulatory effects of herbal products. Am Surg 2002;68:860-864.

Wilkinson A, Davidson J, Dotta F, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation. Clin Transplant 2005;19:291-298.

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

20

Psychosocial and Financial Aspects of Transplantation

Mara Hersh Rifkin

The diagnosis of advancing kidney disease is life changing, not only for the patient, but also for family members. Many questions and concerns may arise that can be addressed by the social worker who is highly invested in patient care and treatment, including the following:

- What treatment choice is best for me?
- How will my life change because of my illness?
- How will my illness affect my family?
- How will I pay for my treatments?
- Will I be able to continue working and return to my daily activities?

ROLE OF THE TRANSPLANTATION SOCIAL WORKER

Clinical social workers, who are licensed and have a masters degree in social work, play a key role before and after kidney transplantation. After patients are referred to the transplantation center, they are scheduled for a pretransplantation evaluation to afford the patient, caregiver, and family members an opportunity to obtain sufficient information to maximize the possibility of a successful outcome. In the United States, the Center for Medicare Services (CMS) guidelines for social services state that the transplantation center must make social services available, facilitated by qualified social workers, to transplant recipients, living donors, and their families.

The transplantation social worker meets with the patient and family members to assess important psychosocial factors, which could significantly affect the outcome of the transplant. These factors include adequacy of support, adherence, substance use, psychiatric status, access to resources, and the ability to understand and cope with the changes in health status, prognosis, and treatment options. If a patient is experiencing

a significant psychosocial problem, the patient may not be approved for transplantation until this issue is addressed. Table 20.1 identifies the areas that should be covered in a comprehensive psychosocial assessment and the availability of community resources.

When a patient is admitted to the hospital for kidney transplantation, the clinical social worker assists both the patient and family in coping with the emotional, psychosocial, and financial aspects of post-transplantation care. Outpatient clinical social work services are also often available to patients and their family members. The transplantation social worker can help patients understand and cope with their feelings and adjust to a new way of life with a kidney transplant. They can assist patients in resolving issues surrounding employment, finances, insurance, and role changes in relationships, issues with sex and intimacy, and concerns about death and dying. In this chapter many of the specific recommendations relate to the care of transplant recipients residing in the United States.

The clinical social worker on the transplantation team is an expert on community resources and can refer patients and family members to the appropriate community resources they might need, such as disability insurance, Social Security, vocational rehabilitation, home care and medical equipment, support groups, and financial resources.

TABLE 20.1 Major Areas Covered in Psychosocial Assessment

Illness Assessment

1. Illness history and impact on patient's functioning, understanding, reaction, and adjustment
2. Patient's knowledge of transplantation, process of being referred to transplant center, understanding of the assessment process for candidacy, feelings about transplantation

Patient Assessment

Personal

Age, life cycle stage

Physical functioning

Intellectual functioning

Emotional functioning

Sexual functioning

Major stressful events

Coping style and approaches

Religious beliefs and faith

History of substance abuse

Ability to comply with medical regime

Educational

Level of education attained

Type of Occupation

Length of employment

Stability of present or recent job

Financial

Sources of income and other resources, their adequacy for current lifestyle, and their adequacy for transplantation and for future medical needs

Support System Assessment

Family

Composition—spouse and children; age, education, occupation; needs, availability

Role structure—effect of illness on roles

Interactions—patterns and quality of communication

Functioning—quality of family life

Problem-solving approach and skills

Social

Extended family—quality of contacts

Friends, neighbors, colleagues—quality of relationships

Others—religious, cultural, and social affiliations

Environmental

Housing and transportation

	Need for relocation
	Need for travel alternatives

PSYCHOSOCIAL BENEFITS OF TRANSPLANTATION

The quality of life for transplant recipients is generally better than the quality of life for dialysis patients. About 80% of transplant recipients function psychosocially at normal levels, compared with 50% of dialysis patients. Dialysis patients show more morbidity on the General Health Questionnaire (which evaluates loss of emotional control and depression) than do transplant recipients and healthy controls. These studies, however, do not address transplant failure, which may result in a significant decrease in quality of life.

The obvious benefit of kidney transplantation is freedom from the constraints of dialysis. Successful transplantation permits much more personal time for an individual who is freed from the necessity of being connected to a dialysis machine for several hours 3 times a week at a dialysis facility or daily home peritoneal dialysis. Recent advances in home hemodialysis have allowed individuals more freedom to dialyze at home on their own schedules, but all these treatments remain time consuming. On average, patients spend anywhere from 40 to 50 hours a month on hemodialysis, 60 to 70 hours on continuous ambulatory peritoneal dialysis (CAPD), 280 hours on continuous cycling peritoneal dialysis (CCPD), or 50 hours on self-care home hemodialysis treatments. There are also significant psychosocial stressors associated with dialysis, including issues surrounding machine dependence, the ability to maintain full-time employment, loss of spontaneity, and reduced time for family activities.

Transplantation permits greater flexibility and more convenience when traveling. Patients do not have the stress of arraigning transient hemodialysis treatments in other cities ahead of time. Transplant offers the freedom to actually plan a vacation or take urgent business trips. Many patients have reported that they have not taken an extended trip since commencing dialysis because of inconvenience and concerns about being too far away from their home dialysis centers or dialyzing at an unfamiliar dialysis center. There is also greater dietary flexibility (see Chapter 19) with kidney transplantation. Fluid restrictions are often difficult for dialysis patients to adhere to in warmer climates and during the summer. Patients can also find it difficult to follow the dietary restrictions necessitated by being on dialysis.

Transplant recipients generally have more energy and stamina and can spend more time dealing with issues outside of their own health problems. The time alone saved in

being off dialysis is about 50 hours per month, or 600 hours per year. This can result in increased earning potential and increased family and personal time. The long-term complications of dialysis may be avoided (see Chapter 1), and many patients view a transplant as a symbol of freedom and restored health.

Ideally, after receiving a kidney transplant, patients are able to return to normal functioning by going back to work or school and getting off of disability. Patients are encouraged to engage in vocational rehabilitation while they are on dialysis because the waiting time for a deceased donor transplant may be years, during which time they may complete training courses or school programs. Social Security offers programs for vocational training and trial work programs that patients can take advantage of while they are receiving disability benefits, and assists with job placement to help individuals get back into the workforce when they are medically able to do so.

Financial Benefits of Transplantation

Relative to individuals who are suffering from other medical conditions, patients with chronic kidney disease in need of dialysis or transplantation receive special treatment in the United States health care system. Since 1972, patients with kidney failure have been eligible for subsidized public health

---

insurance conditional only on their disease status, regardless of age, income, or functional status. This federal Medicare program, which otherwise provides coverage only to individuals who are 65 years and older and those with other qualifying disabilities such as blindness or terminal cancer, also covers patients with kidney failure. Individuals who are in need of kidney transplantation are eligible for Medicare at the time of the transplantation as well as before transplantation if they are on dialysis.

Successful kidney transplantation is more cost-effective than hemodialysis and provides a relative net savings after a period of about 3 years. Although data may vary from center to center, transplantation costs to Medicare average $103,000 by the end of the first year, with cumulative costs decreasing each successive year, as a consequence of avoidance of dialysis and reduction in dosage of immunosuppressive drugs. The reduction continues so that the cumulative cost is about $120,000 by the end of the second year, and $137,000 by the end of the third year. These costs do not reflect the costs associated with rehospitalization (beyond the first year). The cost of providing in-center hemodialysis is about $70,000 per year. Therefore, kidney transplantation is a more cost-effective alternative than dialysis if the graft remains viable for more than 2 to 3 years. Depending on donor source, 80% to 90% of transplanted kidneys remain viable long enough to recoup this dividend.

PSYCHOSOCIAL RISKS OF TRANSPLANTATION

There are a number of psychosocial risks and complications associated with kidney

transplantation, just as there are with chronic dialysis. The transplantation social worker can offer support for the patient, family, and significant others with issues that can have a negative effect on transplant results, such as reluctance to leave the dependent “sick role,” concerns about reentering the workforce, importance of being needed rather than needing, and maintenance of hope during periods of rejection.

Although patients are educated about medication side effects, until they are faced with them, it is uncertain how they will cope. Patients who have a prior psychiatric history of anxiety or depression are particularly susceptible to an exacerbation of their symptoms when immunosuppressive therapy begins, although patients with no prior history are also at risk (see Chapter 17). Both patients and family members should be comforted by the assurance that such symptoms are generally temporary and treatable. The physical side effects of some transplant medications, such as hirsutism, gum overgrowth, and potential weight gain, may affect body image in a manner that is not always easily detectable, and sensitive probing may be required. Side effects are almost inevitable after transplantation and can cause medication noncompliance. Patients should be systematically questioned about their attitude toward their side effects. Patients can ameliorate some of the side effects of medications with careful attention to diet and exercise, and team members should promote empowerment to do so, rather than promote an expectation of inevitability.

Multiple lifestyle changes occur for the transplant recipient. Their place may change within their family system and work environment. Their capacity to reenter the workforce after many years may be changed. There may be a risk for losing financial support, such as disability income and health insurance. Personal relationships may be at risk, and post-transplantation stress may lead to divorce and separation. Sexual functioning may change after transplantation (see Chapter 10) and engender new hopes and fears. The newly found post-transplantation freedom may be a threat to patients whose identity has been associated with their “sick role” as a dialysis patient. Some dialysis patients

create a social network at their dialysis units, and transplantation can disrupt this connection.

The shift to health may be difficult, and an identity crisis may occur. Counseling and support groups can aid in this transition. Employment is a topic that weighs heavily on many patients who have been receiving disability payment from various sources and is often tied into their health insurance coverage. There can be fear of losing Medicare or Medicaid benefits and not being able to obtain health insurance from a new employer. Government legislation (the Ticket to Work and Work Incentives Act of 1999, known as “the ticket” and the Health Insurance Portability and Accountability Act, or HIPAA) offers some protection for transplant recipients who face this hurdle.

Many patients live in fear of suffering rejection episodes and losing their transplants, or suffering from other catastrophic complications. These fears are not irrational,

although they may be exaggerated; they can be best addressed by an open and factual discussion of the extent of the risk at all phases of treatment. Patients may also suffer feelings of guilt at having received a kidney at someone else's expense. Patients should be assured that these are common feelings and reminded that they are deserving beneficiaries of the wishes of the donor and the donor's loved ones.

NONADHERANCE AND NONCOMPLIANCE

Graft survival is dependent on providing adequate long-term pharmacologic immunosuppression and the maintenance of sometimes onerous regimes of medical follow-up and health-promoting behavior. As a consequence, transplant recipients who do not adhere to often complex medical regimens are at substantial risk for graft loss. The terms *noncompliance* and *nonadherence* are used to indicate failure of transplant recipients to behave in a manner that best promotes the function of their transplant. Few patients consciously decide to behave in such a manner. For most, noncompliant or nonadherent behavior evolves gradually as a consequence of many interacting variables.

Noncompliance with medical therapies affects treatment outcomes in many chronic diseases, and it is estimated that only half of the 1.6 billion prescriptions written in the United States each year are taken properly. To quote former surgeon general Dr. C. Everett Koop, “Drugs don't work in patients who don't take them!” A series of variables have been linked to medication noncompliance (Table 20.2), and each is evident in transplant immunosuppressant regimens. In renal transplantation, clinically important medication noncompliance occurs in about 20% of recipients, substantially increasing the risk for adverse immunologic events and even death. Occasional noncompliance and “forgetfulness” are widespread, although their clinical significance is difficult to assess. Both multiple and late episodes of acute rejection predict subsequent graft loss (see Chapter 10), and medication noncompliance significantly enhances the risk for both. Noncompliance greatly increases the risk for graft loss and is a contributing factor in more than one third of cases of graft loss.

Several demographic variables appear to affect the likelihood of noncompliance. Diabetic patients, accustomed to the demands of living with chronic illness, are less likely to have problems with compliance after transplantation. Younger patients, particularly adolescents, and those with a limited educational background are more likely to be noncompliant (see Chapter 16). Psychiatric illness and a history of substance abuse also increase risk. At least some noncompliant behavior is attributable to either financial hardship or the relative inability to procure appropriate medication when no funds are available. Low socioeconomic status is a strong predictor of noncompliance and poorer long-term outcomes in renal transplantation. Knowledge of these demographic risk

---

factors, however, is of only limited benefit in dealing with individual patients. It does

little to facilitate identification of noncompliant behavior early enough to allow remedy, nor does it provide insight into what that remedy should be.

TABLE 20.2 Attributes of Pharmacologic Therapies that Enhance the Risk for Noncompliance

Multiple medications
Prolonged duration of therapy
Short dosing intervals
Palatability of medication
Definable adverse effects
Financial expense
Beliefs about severity of illness
Failure to understand treatment regimen
Increasing intervals between contacts with providers

Adapted from Cramer JA. Practical issues in medication compliance. Transplant Proc 1999;31(Suppl 4A):7S-9S.

The interventions required to alter noncompliant behavior vary from patient to patient. At the very least, transplant recipients must have access to immunosuppressants, the annual cost of which may exceed that of housing for many patients (Table 20.3). For patients with private insurance or Medicaid coverage, finances may not pose a significant problem. Medicare policy now provides immunosuppressant coverage for the life of the allograft, but only for those beneficiaries who retain Medicare eligibility beyond the 3 years allowed for end-stage renal disease (ESRD) patients after transplantation. Other patients must navigate (usually with the assistance of social workers) a complex network of indigent care programs and state kidney networks. There is a significant risk for late rejection and graft loss for patients who discontinue immunosuppressant medications because of financial hardship; when patients are provided with drugs, outcomes improve dramatically. In the 1990s, extension of Medicare coverage for immunosuppressants for 1 to 3 years was shown to attenuate income-related differences in long-term graft survival.

TABLE 20.3 Financial Costs of Commonly Used Oral Immunosuppressive Medications in the United States

Immunosuppressive	Cost per Annum*
Tacrolimus	$ 15,000
Cyclosporine, microemulsion solution	$ 13,700
Cyclosporine, generic, capsules	$ 12,400

Mycophenolate mofetil	$ 12,100
Mycophenolic acid, delayed release	$ 10,300
Sirolimus	$ 10,900
Prednisone	$ 160
Azathioprine	$ 900

* Approximate annual charges (for an average patient weighing 70 kg, at a retail pharmacy in Los Angeles, CA, 2008). Note that most transplantation centers use a combination of two or three of the immunosuppressive medications listed.

In addition to ensuring financial access to proper medications, other interventions might improve patient compliance. Electronic monitoring of drug dosing can allow earlier detection of noncompliance, although such devices have not become widely accepted. Drug regimens should be simplified, with perhaps optimal compliance as a more compelling goal than optimal pharmacokinetics. Patients should be helped to develop daily routines that foster compliance. The facilitation of adherence of transplant recipients to their medical regimen requires both recognition of its importance in ensuring long-term graft survival and ongoing trust between patient and provider.

DISABILITY INSURANCE FOR TRANSPLANT RECIPIENTS IN THE

UNITED STATES

State Disability Insurance

In some states, state disability insurance (SDI) is available for patients who are employed and are paying state income taxes. Patients are also eligible to apply if they are unable to work because of disabilities that are not work related (e.g., while they are receiving medical treatments or recovering from illness, surgery, or non-work-related accidents). SDI eligibility begins 1 week after the patient stops work for any of the above reasons, and continues for a maximum of 1 year, or until the patient is able to return to work, or until their SDI funds run out (usually up to 6 months). Patients who continue to be disabled after 1 year need to apply for long-term disability. The maximum financial benefit is based on the individual's highest quarter wage. It is often supplemented by employer disability plans to approximate the original salary.

For transplant recipients, the estimated amount of time off work is 2 to 3 months, although some patients may return to work sooner. Because transplant recipients require close medical follow-up in the first 1 to 2 months, it is generally recommended that they do not return to work before 2 months after transplantation. Some patients are unable to cope financially on SDI for more than 1 month, and request to return to work sooner. A decision needs to be made about whether the patient is medically stable and can be cleared to return to work.

Family members who care for transplant recipients during their recovery may be eligible for family leave; this may be paid or unpaid leave, depending on their employer, whether they paid into SDI, or if they have a private disability benefit. Individuals are encouraged to investigate SDI eligibility, private disability benefits, and family leave benefits in advance of kidney transplantation, so they can be educated and more prepared financially after transplantation.

Social Security Disability Income

Social Security disability income (SSDI) is long-term disability program for patients who are considered “permanently” disabled for at least 1 year. Patients who run out of temporary disability and yet are still unable to return to work often apply for SSDI, even before 1 year of being disabled, because the eligibility process can take several months.

Social Security payments are monthly and are based on a patient's individual earnings in the highest quarter. Patients with ESRD who are on dialysis or who have undergone transplantation are eligible for Social Security disability if they have paid Federal Insurance Contributions Act (FICA) taxes. Patients are encouraged to continue working even after starting on dialysis because they may be able to have flexible work hours or reduce their work schedule to part-time. Patients may choose home hemodialysis or peritoneal dialysis so as not to interrupt their work schedules by having to go to a

hemodialysis center several times a week. Patients receiving SSDI may return to work on a limited

basis without having their Social Security benefits stopped. They can still collect SSDI as long as they do not earn more than $670 per month for more than 8 months.

Patients should be encouraged to return to work after a transplantation because many will lose their benefits and insurance. Some patients continue on SSDI, particularly if they have disabling conditions in addition to ESRD (e.g., diabetes, retinopathy, blindness, or other physical disabilities).

Consolidated Budget Reconciliation Act of 1985

The Consolidated Budget Reconciliation Act (COBRA) of 1985 provides additional help to employees and their dependents who would normally lose their health insurance coverage because of job loss, divorce, or the death or retirement of a spouse. This is a federal law that requires companies with 20 or more employees to extend their insurance coverage to employees and their dependents for 18 months (up to 36 months) when benefits would otherwise end. Although patients may receive extended coverage through COBRA, they are still fully responsible for premium payments to the group health plan.

An employee covered by a group health plan may continue coverage for up to 18 months if the employee left work voluntarily or involuntarily (for reasons other than misconduct), or the working hours are reduced beyond the minimum amount to qualify for health benefits. Patients considered disabled under Social Security guidelines at the time work is discontinued can choose to continue their health coverage for up to 29 months, after which time they become eligible for Medicare. They must show that they are insurable in order to continue coverage. If a person leaves work because of disability, they may be able to keep their life insurance policy if there is a disability waiver. The insurer must be notified and proof of disability provided.

Family Medical Leave Act

The Family Medical Leave Act (FMLA) requires employers to provide up to 12 weeks of unpaid job-protected leave to “eligible” employees for certain family and medical reasons that make the employees unable to perform their work. Employees are eligible if they have worked for an employer for at least 1 year (minimum of 1250 hours over the previous 12 months).

The employee may be required to provide advance leave notice and medical certification. Leave may be denied if requirements are not met. The employee ordinarily must provide 30 days' advance notice when leave is “foreseeable.” An employer may require a medical certificate (and may require a second opinion at the employer's expense) to support a request for leave because of a serious health

condition. For the duration of FMLA leave, the employer must maintain the employee's health coverage under any “group health plan.” Upon return from FMLA leave, most employees must be restored to their original or equivalent positions with equivalent pay, benefits, and other employment terms. The use of FMLA leave cannot result in the loss of any employment benefit that accrued before the start of an employee's leave. The U.S. Department of Labor is authorized to investigate and resolve complaints of violations. An eligible employee may bring a civil action against an employer for violations.

Vocational Rehabilitation

Successful kidney transplantation enhances the physical and mental quality of life for many individuals. With improved health and stamina, transplant recipients may be more willing to reenter the workforce, enter a vocational training program, or return to school. Many transplant patients are not working at the time of the transplantation for various health reasons. They may be eligible for vocational rehabilitation, as are patients who are unable to return to their prior employment because their job responsibilities are in conflict with transplant-related restrictions.

Vocational rehabilitation is a service that provides people with disabilities the tools they need to be able to return to work, enter a new line of work, maintain work, or start work for the first time. After a transplantation, it is important that the patient enter a rehabilitation program as soon as the patient is well is able to work, in order to protect their disability coverage. The Social Security Administration (SSA) can help people with disabilities get the vocational rehabilitation services they need. Patients need to inquire at their local SSA office about these services; they may also contact their state rehabilitation agency. Vocational rehabilitation providers furnish a variety of services designed to provide the training or other services that are needed to help patients acquire gainful employment.

When a person is able to successfully return to work, special rules, called “work incentives,” help them retain their current cash benefits (SSDI, SDI) and health insurance coverage (Medicare, Medicaid) during a trial work period. There are different work incentives for people who receive SSDI and SDI benefits. These incentives help people with disabilities to work by allowing them to test their ability to work for a specified period of time without losing any benefits.

Selected Readings

Bohlke M, Marini SS, Gomes RH, et al. Predictors of employment after successful kidney transplantation: a population-based study. Clin Transplant 2008;22:405-410.

Butler JA, Roderick P, Muller M, et al. Frequency and impact of non-adherence to immunosuppressants after renal transplantation: a systematic review. Transplantation 2004;77:769-789.

Chapman JR. Compliance: the patient, the doctor, and the medication. Transplantation 2004;77:782-785.

Council of Nephrology Social Workers, Kidney Transplantation. A Primer for Nephrology Social Workers. New York: National Kidney Foundation, 2006.

Gaston RS, Hudson SL, Ward M, et al. Late allograft loss: noncompliance masquerading as chronic rejection. Transplant Proc 1999;31(Suppl 4A):21S-23S.

Greenstein S, Siegal B. Evaluation of a multivariate model predicting noncompliance with medication regimens among renal transplant patients. Transplantation 2000;69:2226-2228.

Hirth RA. The organization and financing of kidney dialysis and transplant care in the United States of America. Int J Health Care Finance Econ 2007;7:301-318.

Markell MS, DiBenedetto A, Maursky V, et al. Unemployment in inner-city renal transplant recipients: predictive and sociodemographic factors. Am J Kidney Dis 1997;29:881-887.

Prieto LR, Miller DS, Gayowski T, et al. Multicultural issues in organ transplantation: the influence of patients' cultural perspectives on compliance with treatment. Clin Transpl 1997;11:529-535.

Thamer M, Henderson SC, Fox Ray N, et al. Unequal access to cadaveric transplantation in California based on insurance status. Health Serv Res 1999;34:879-884.

U.S. Renal Data System (USRDS). Annual Data Report: Atlas of end-stage renal disease in the United States. Bethesda, MD: National Institutes of Diabetes and Digestive and Kidney Diseases, 2005.

Woodward RS, Schnitzler MA, Lowell JA, et al. Effect of extended coverage of immunosuppressive medications by Medicare on the survival of cadaveric renal transplants. Am J Transplant 2001;1:69-73.

APPENDIX

The Declaration of Istanbul on Organ Trafficking and Transplant Tourism

PREAMBLE

Organ transplantation, one of the medical miracles of the 20th century, has pro-longed and improved the lives of hundreds of thousands of patients worldwide. The many great scientific and clinical advances of dedicated health professionals, as well as countless acts of generosity by organ donors and their families, have made transplantation not only a life-saving therapy but also a shining symbol of human solidarity. Yet these accomplishments have been tarnished by numerous reports of trafficking in human beings who are used as sources of organs and of patient-tourists from rich countries who travel abroad to purchase organs from poor people. In 2004, the World Health Organization called on member states “to take measures to protect the poorest and vulnerable groups from transplant tourism and the sale of tissues and organs, including attention to the wider problem of international trafficking in human tissues and organs” (1).

To address the urgent and growing problems of organ sales, transplant tourism and trafficking in organ donors in the context of the global shortage of organs, a Summit Meeting of more than 150 representatives of scientific and medical bodies from around the world, government officials, social scientists, and ethicists was held in Istanbul from April 30 to May 2, 2008. Preparatory work for the meeting was undertaken by a Steering Committee convened by the Transplantation Society (TTS) and the International Society of Nephrology (ISN) in Dubai in December 2007. That committee's draft declaration was widely circulated and then revised in light of the comments received. At the Summit, the revised draft was reviewed by working groups and finalized in plenary deliberations.

This Declaration represents the consensus of the Summit participants. All countries need a legal and professional framework to govern organ donation and transplantation activities, as well as a transparent regulatory oversight system that ensures donor and recipient safety and the enforcement of standards and prohibitions on unethical practices.

Unethical practices are, in part, an undesirable consequence of the global shortage of organs for transplantation. Thus, each country should strive both to ensure that programs to prevent organ failure are implemented and to provide organs to meet the transplant needs of its residents from donors within its own population or through regional cooperation. The therapeutic potential of deceased organ donation should be maximized not only for kidneys but also for other organs, appropriate to the transplantation needs of each country. Efforts to initiate or enhance deceased donor transplantation are essential to minimize the burden on living donors. Educational programs are useful in addressing the barriers, misconceptions, and mistrust that currently impede the development of sufficient deceased donor transplantation; successful transplantation programs also depend on the existence of the relevant health system infrastructure.

Access to health care is a human right but often not a reality. The provision of care for living donors before, during, and after surgery-as described in the reports of the international forums organized by TTS in Amsterdam and Vancouver (2,3,4)—is no less essential than taking care of the transplant

recipient. A positive outcome for a recipient can never justify harm to a live donor; on the contrary, for a transplant with a live donor to be regarded as a success means that both the recipient and the donor have done well.

This Declaration builds on the principles of the Universal Declaration of Human Rights (5). The broad representation at the Istanbul Summit reflects the importance of international collaboration and global consensus to improve donation and transplantation practices. The Declaration will be submitted to relevant professional organizations and to the health authorities of all countries for consideration. The legacy of transplantation must not be the impoverished victims of organ trafficking and transplant tourism but rather a celebration of the gift of health by one individual to another.

DEFINITIONS

Organ trafficking is the recruitment, transport, transfer, harboring, or receipt of living or deceased persons or their organs by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability, or of the giving to, or the receiving by, a third party of payments or benefits to achieve the transfer of control over the potential donor, for the purpose of exploitation by the removal of organs for transplantation (6).

Transplant commercialism is a policy or practice in which an organ is treated as a commodity, including by being bought or sold or used for material gain.

Travel for transplantation is the movement of organs, donors, recipients, or transplant professionals across jurisdictional borders for transplantation purposes. Travel for transplantation becomes transplant tourism if it involves organ trafficking and/or

transplant commercialism or if the resources (organs, professionals, and transplant centers) devoted to providing transplants to patients from outside a country undermine the country's ability to provide transplant services for its own population.

PRINCIPLES

1. National governments, working in collaboration with international and nongovernmental organizations, should develop and implement comprehensive programs for the screening, prevention, and treatment of organ failure, which include:

- The advancement of clinical and basic science research;
- Effective programs, based on international guidelines, to treat and maintain patients with end-stage diseases, such as dialysis programs for renal patients, to minimize morbidity and mortality, alongside transplantation programs for such diseases;
- Organ transplantation as the preferred treatment for organ failure for medically suitable recipients.

2. Legislation should be developed and implemented by each country or jurisdiction to govern the recovery of organs from deceased and living donors and the practice of transplantation, consistent with international standards.

- Policies and procedures should be developed and implemented to maximize the number of organs available for transplantation, consistent with these principles;
- The practice of donation and transplantation requires oversight and accountability by health authorities in each country to ensure transparency and safety;
- Oversight requires a national or regional registry to record deceased and living donor transplants;
- Key components of effective programs include public education and awareness, health professional education and training, and defined responsibilities and accountabilities for all stakeholders in the national organ donation and transplant system.

3. Organs for transplantation should be equitably allocated within countries or jurisdictions to suitable recipients without regard to gender, ethnicity, religion, or social or financial status.

- Financial considerations or material gain of any party must not influence the application of relevant allocation rules.

4. The primary objective of transplant policies and programs should be optimal short- and long-term medical care to promote the health of both donors and recipients.

. Financial considerations or material gain of any party must not override primary consideration for the health and well-being of donors and recipients.

5. Jurisdictions, countries, and regions should strive to achieve self-sufficiency in organ donation by providing a sufficient number of organs for residents in need from within the country or through regional cooperation.

. Collaboration between countries is not inconsistent with national self- sufficiency as long as the collaboration protects the vulnerable, promotes equality between donor and recipient populations, and does not violate these principles;

. Treatment of patients from outside the country or jurisdiction is only acceptable if it does not undermine a country's ability to provide transplant services for its own population.

6. Organ trafficking and transplant tourism violate the principles of equity, justice, and respect for human dignity and should be prohibited. Because transplant commercialism targets impoverished and otherwise vulnerable donors, it leads inexorably to inequity and injustice and should be prohibited. In Resolution 44.25, the World Health Assembly called on countries to prevent the purchase and sale of human organs for transplantation.

. Prohibitions on these practices should include a ban on all types of advertising (including electronic and media), soliciting, or brokering for the purpose of transplant commercialism, organ trafficking, or transplant tourism.

. Such prohibitions should also include penalties for acts-such as medically screening donors or organs, or transplanting organs-that aid, encourage, or use the products of organ trafficking or transplant tourism.

. Practices that induce vulnerable individuals or groups (such as illiterate and impoverished persons, undocumented immigrants, prisoners, and political or economic refugees) to become living donors are incompatible with the aim of combating organ trafficking, transplant tourism, and transplant commercialism.

PROPOSALS

Consistent with these principles, participants in the Istanbul Summit suggest the following strategies to increase the donor pool and to prevent organ trafficking,

transplant commercialism, and transplant tourism and to encourage legitimate, life-saving transplantation programs.

To respond to the need to increase deceased donation:

1. Governments, in collaboration with health care institutions, professionals, and nongovernmental organizations, should take appropriate actions to increase deceased organ donation. Measures should be taken to remove obstacles and disincentives to deceased organ donation.

2. In countries without established deceased organ donation or transplantation, national legislation should be enacted that would initiate deceased organ donation and create transplantation infrastructure, so as to fulfill each country's deceased donor potential.

3. In all countries in which deceased organ donation has been initiated, the therapeutic potential of deceased organ donation and transplantation should be maximized.

4. Countries with well-established deceased donor transplant programs are encouraged to share information, expertise, and technology with countries seeking to improve their organ donation efforts.

To ensure the protection and safety of living donors and appropriate recognition for their heroic act while combating transplant tourism, organ trafficking and transplant commercialism:

1. The act of donation should be regarded as heroic and honored as such by representatives of the government and civil society organizations.

2. The determination of the medical and psychosocial suitability of the living donor should be guided by the recommendations of the Amsterdam and Vancouver Forums (2,3,4).

. Mechanisms for informed consent should incorporate provisions for evaluating the donor's understanding, including assessment of the psychological impact of the process;

. All donors should undergo psychosocial evaluation by mental health professionals during screening.

3. The care of organ donors, including those who have been victims of organ trafficking, transplant commercialism, and transplant tourism, is a critical responsibility of all jurisdictions that sanctioned organ transplants utilizing such practices.

4. Systems and structures should ensure standardization, transparency, and accountability of support for donation.

- Mechanisms for transparency of process and follow-up should be established;
- Informed consent should be obtained both for donation and for follow-up processes.

5. Provision of care includes medical and psychosocial care at the time of donation and for any short- and long-term consequences related to organ donation.

- In jurisdictions and countries that lack universal health insurance, the provision of disability, life, and health insurance related to the donation event is a necessary requirement in providing care for the donor;
- In those jurisdictions that have universal health insurance, governmental services should ensure donors have access to appropriate medical care related to the donation event;
- Health and/or life insurance coverage and employment opportunities of persons who donate organs should not be compromised;

- All donors should be offered psychosocial services as a standard component of follow-up;
- In the event of organ failure in the donor, the donor should receive:
  i. Supportive medical care, including dialysis for those with renal failure, and
  ii. Priority for access to transplantation, integrated into existing allocation rules as they apply to either living or deceased organ transplantation.

6. Comprehensive reimbursement of the actual, documented costs of donating an organ does not constitute a payment for an organ, but is rather part of the legitimate costs of treating the recipient.

- Such cost-reimbursement would usually be made by the party responsible for the costs of treating the transplant recipient (such as a government health department or a health insurer);
- Relevant costs and expenses should be calculated and administered using transparent methodology, consistent with national norms;
- Reimbursement of approved costs should be made directly to the party supplying the service (such as to the hospital that provided the donor's medical care);
- Reimbursement of the donor's lost income and out-of-pockets expenses should be administered by the agency handling the transplant rather than paid directly from the recipient to the donor.

7. Legitimate expenses that may be reimbursed when documented include:

. The cost of any medical and psychological evaluations of potential living donors who are excluded from donation (e.g., because of medical or immunologic issues discovered during the evaluation process);

. Costs incurred in arranging and effecting the pre-, peri- and postoperative phases of the donation process (e.g., long-distance telephone calls, travel, accommodation and subsistence expenses);

. Medical expenses incurred for postdischarge care of the donor;

. Lost income in relation to donation (consistent with national norms).

References

1. World Health Assembly Resolution 57.18, Human organ and tissue transplantation, 22 May 2004, http://www.who.int/gb/ebwha/pdf_files/WHA57/A57_R18-en.pdf.

2. The Ethics Committee of the Transplantation Society (2004). The Consensus Statement of the Amsterdam Forum on the Care of the Live Kidney Donor. Transplantation 78(4):491-92.

3. Barr ML, Belghiti J, Villamil FG, Pomfret EA, Sutherland DS, Gruessner RW, Langnas AN & Delmonico FL (2006). A Report of the Vancouver Forum on the Care of the Life Organ Donor: Lung, Liver, Pancreas, and Intestine Data and Medical Guidelines. Transplantation 81(10):1373-85.

4. Pruett TL, Tibell A, Alabdulkareem A, Bhandari M, Cronon DC, Dew MA, Dib-Kuri A, Gutmann T, Matas A, McMurdo L, Rahmel A, Rizvi SAH, Wright L & Delmonico FL (2006). The Ethics Statement of the Vancouver Forum on the Live Lung, Liver, Pancreas, and Intestine Donor. Transplantation 81(10):1386-87.

5. Universal Declaration of Human Rights, adopted by the UN General Assembly on December 10, 1948, http://www.un.org/Overview/rights.html.

6. Based on Article 3a of the Protocol to Prevent, Suppress and Punish Trafficking in Persons, Especially Women and Children, Supplementing the United Nations Convention Against Transnational Organized Crime, http://www.uncjin.org/Documents/Conventions/dcatoc/final_documents_2/conventio

Color Plates

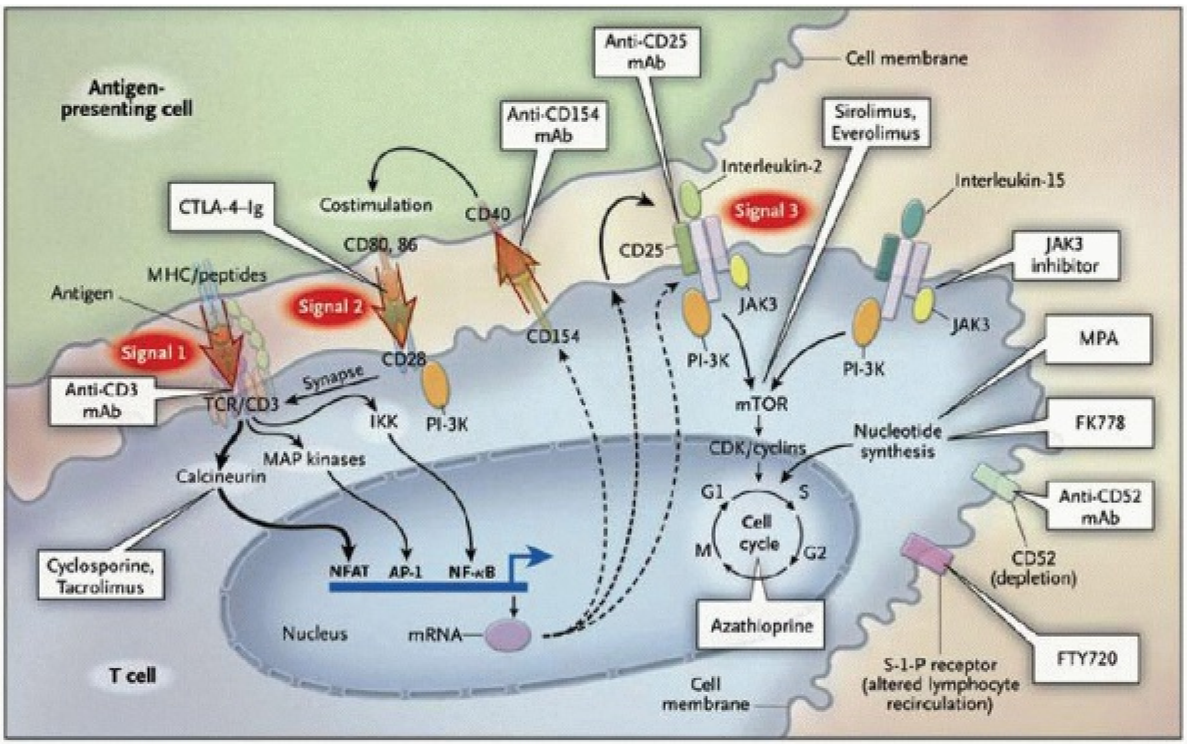


PLATE 5.1 Anti-CD154 antibody, FTY720, and FK778 have been withdrawn from clinical trials. MPA, mycophenolic acid. (From Halloran P. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2005;351:2715-2729, with permission. see black and white image)

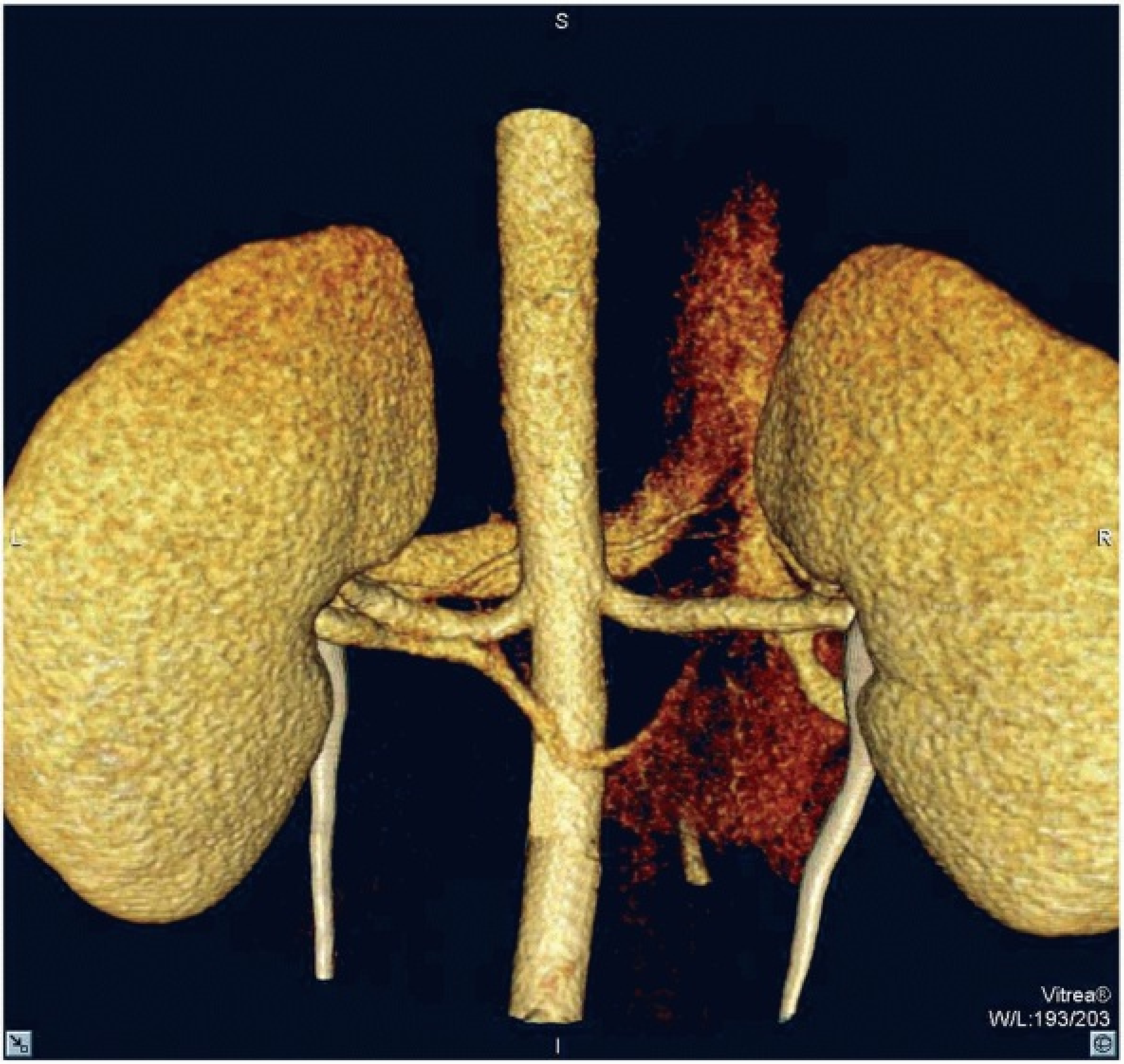


PLATE 13.1 Computed tomographic angiogram of renal arteries with volume-rendered reformation. Posterior vantage with aorta on *left*, demonstrating two left renal arteries. see black and white image

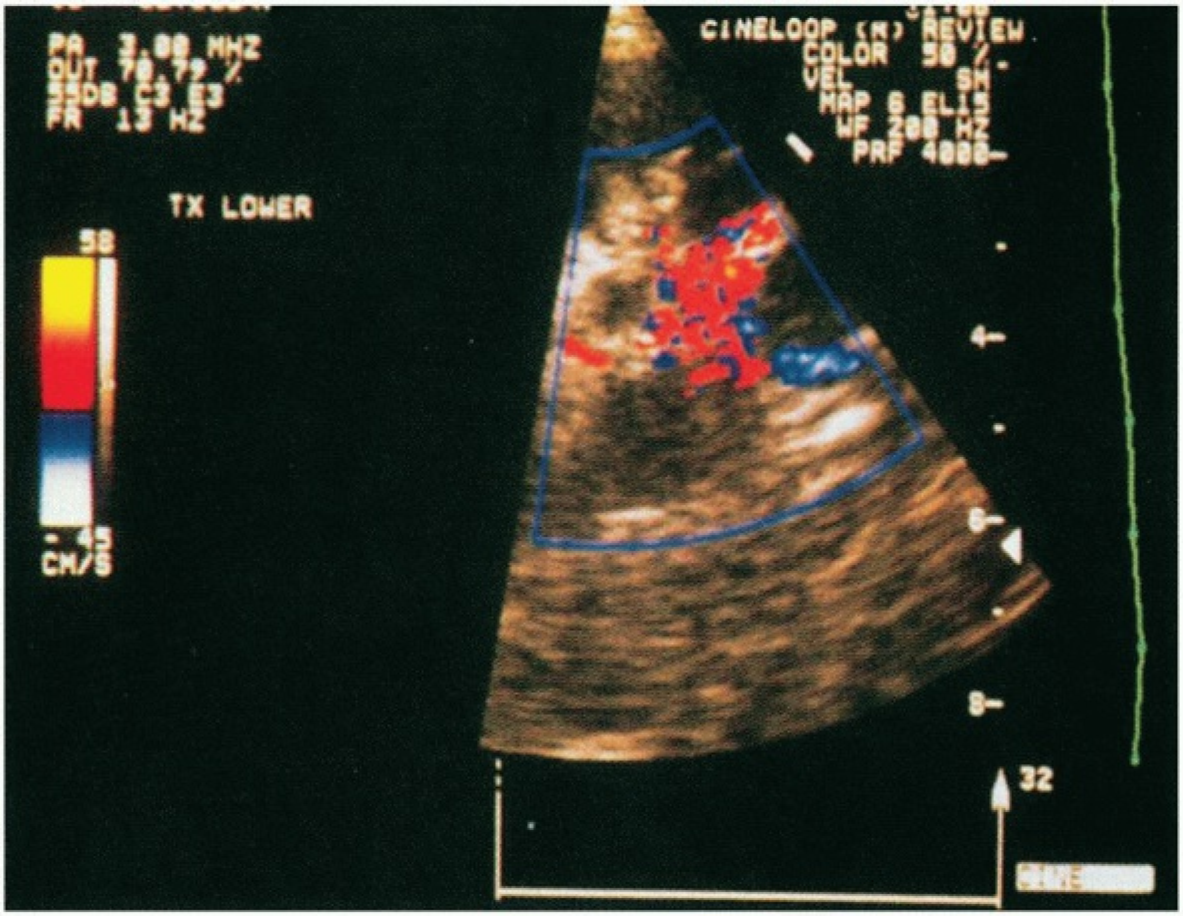


PLATE 13.2 Postbiopsy arteriovenous fistula. Color Doppler image shows an area of random color assignment. Pulsed-gate Doppler analysis revealed high-velocity, lowresistance arterial flow and arterialization of the venous waveform. see black and white image

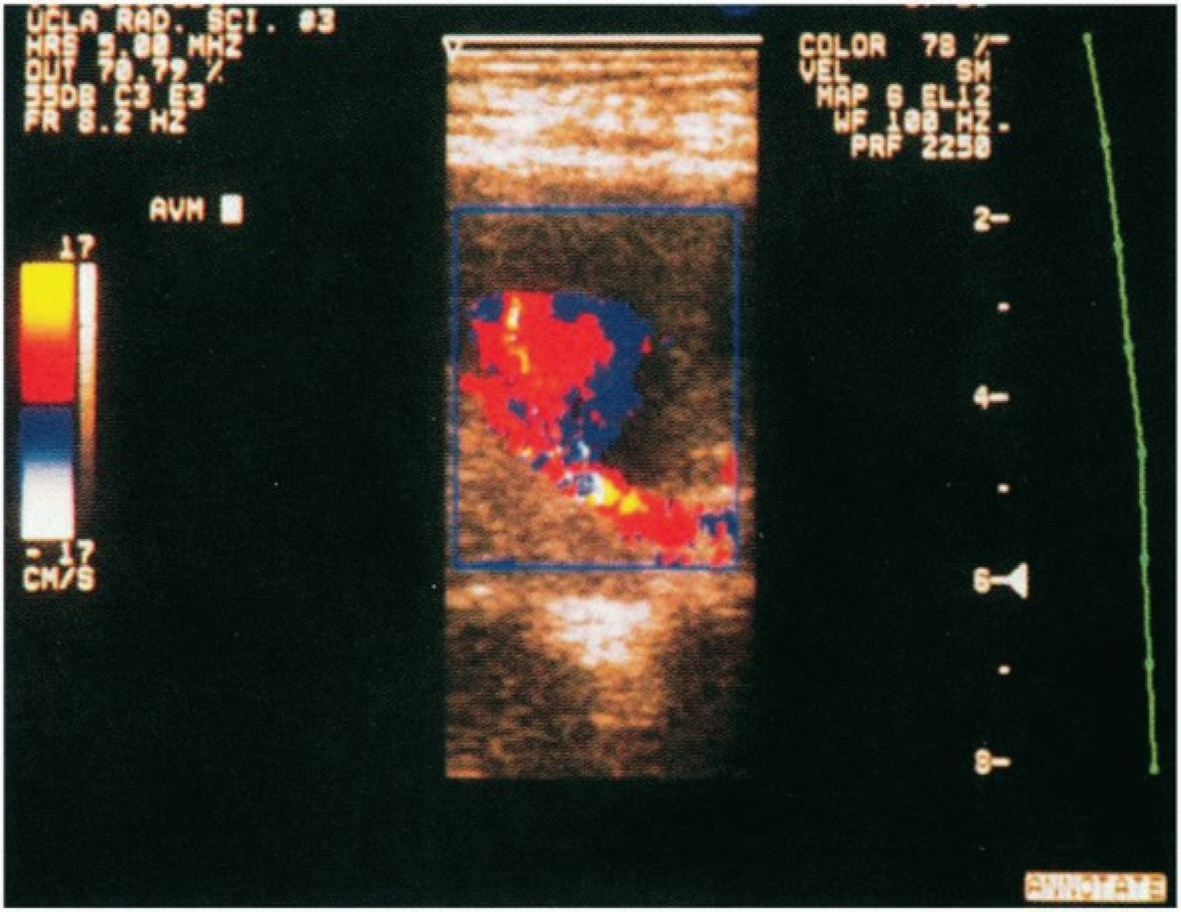


PLATE 13.3 Pseudoaneurysm. Grayscale image demonstrated a cystic lesion, and color Doppler image shows swirling internal flow. see black and white image

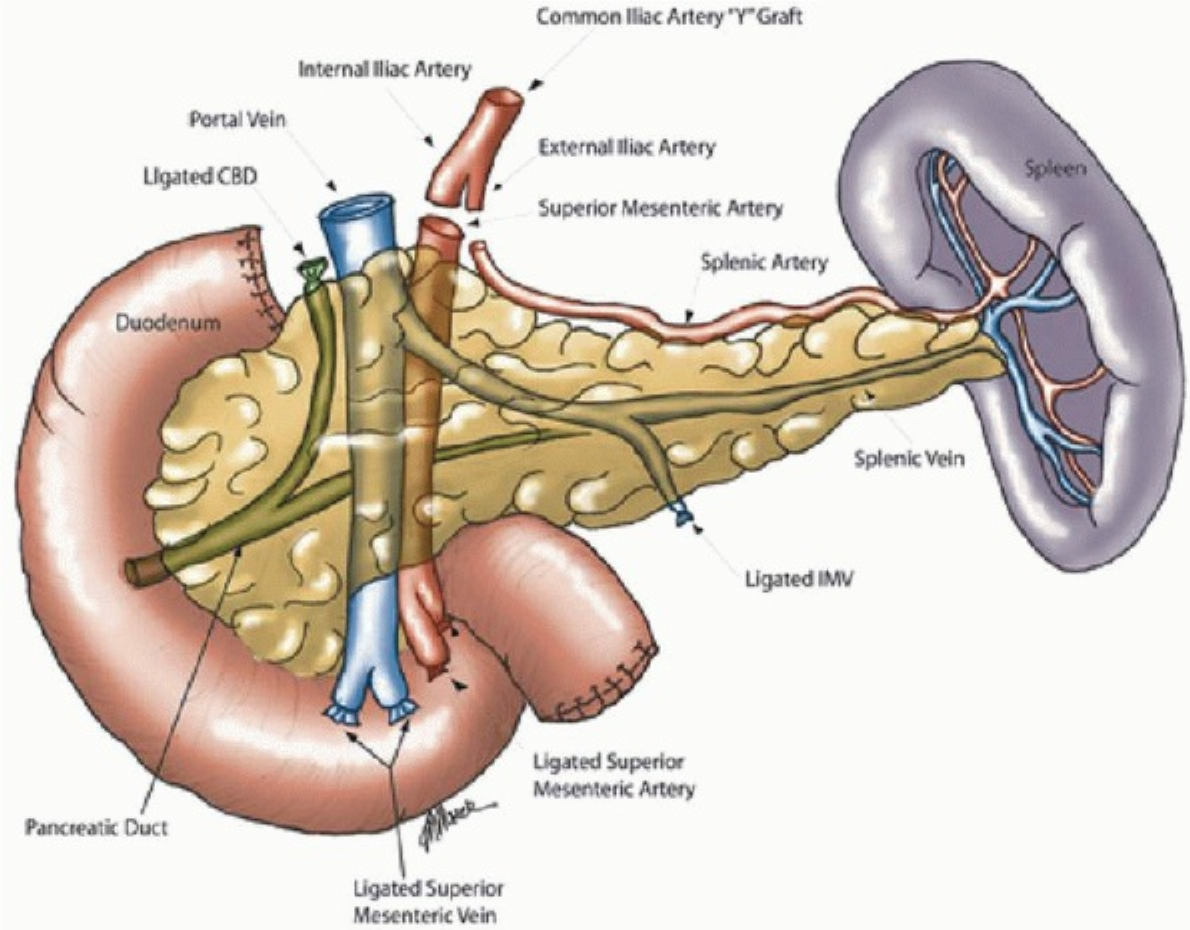


PLATE 15.1 Anatomy of procured pancreatic allograft before backbench preparation. CBD, common bile duct; IMV, inferior mesenteric vein. (From Lipshutz GS, Wilkinson AH. Pancreas-kidney and pancreas transplantation for the treatment of diabetes mellitus. Endocrinol Metab Clin North Am 2007;36:1015-1038, with permission. see black and white image)

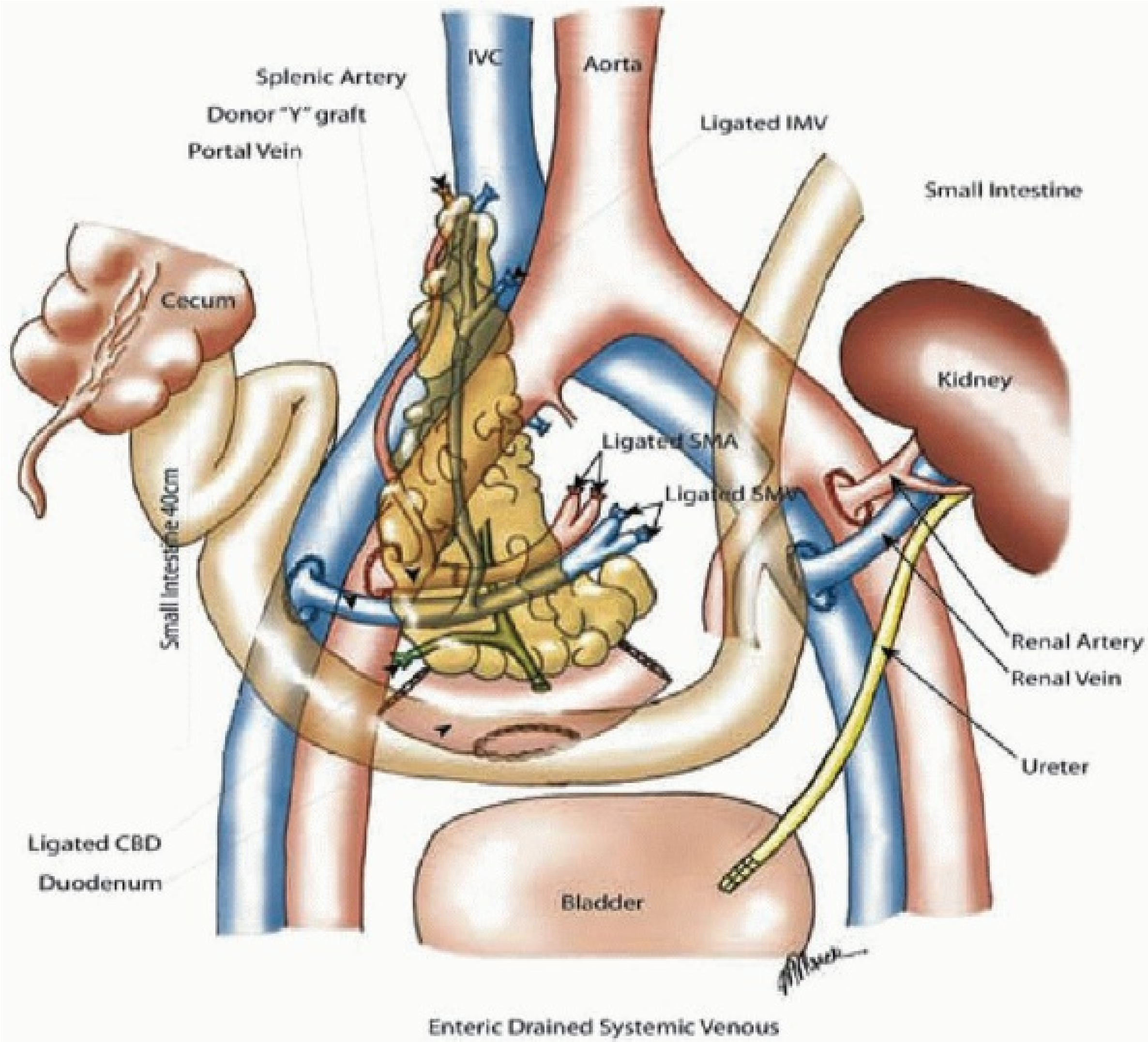


PLATE 15.2 Systemic venous and enteric-drained pancreatic allograft with kidney on the left. (From Lipshutz GS, Wilkinson AH. Pancreas-kidney and pancreas transplantation for the treatment of diabetes mellitus. Endocrinol Metab Clin North Am 2007;36: 1015-1038, with permission. see black and white image)

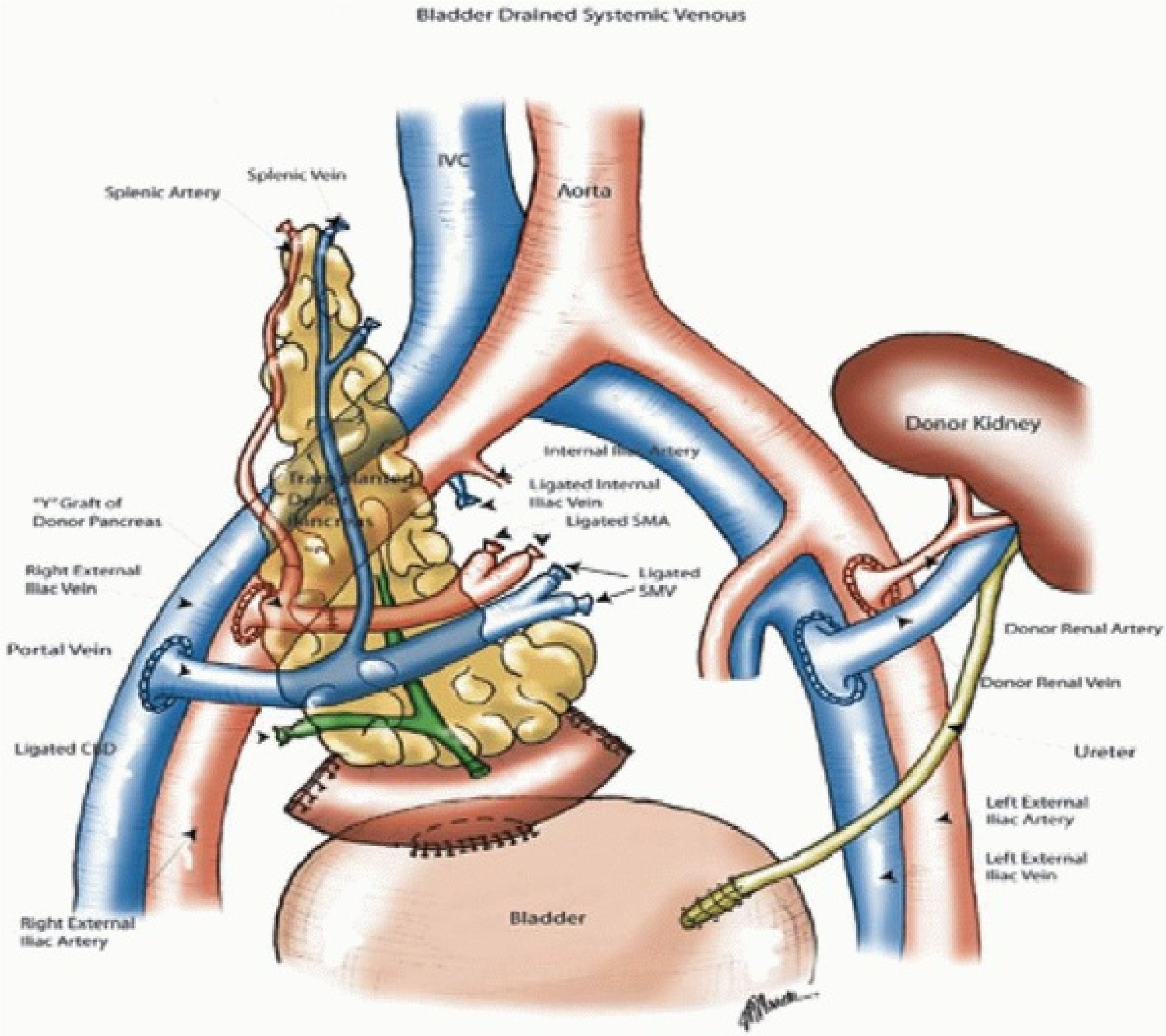


PLATE 15.3 Systemic venous and bladder-drained pancreatic allograft with kidney on the left. (From Lipshutz GS, Wilkinson AH. Pancreas-kidney and pancreas transplantation for the treatment of diabetes mellitus. Endocrinol Metab Clin North Am 2007;36: 1015-1038, with permission. see black and white image)

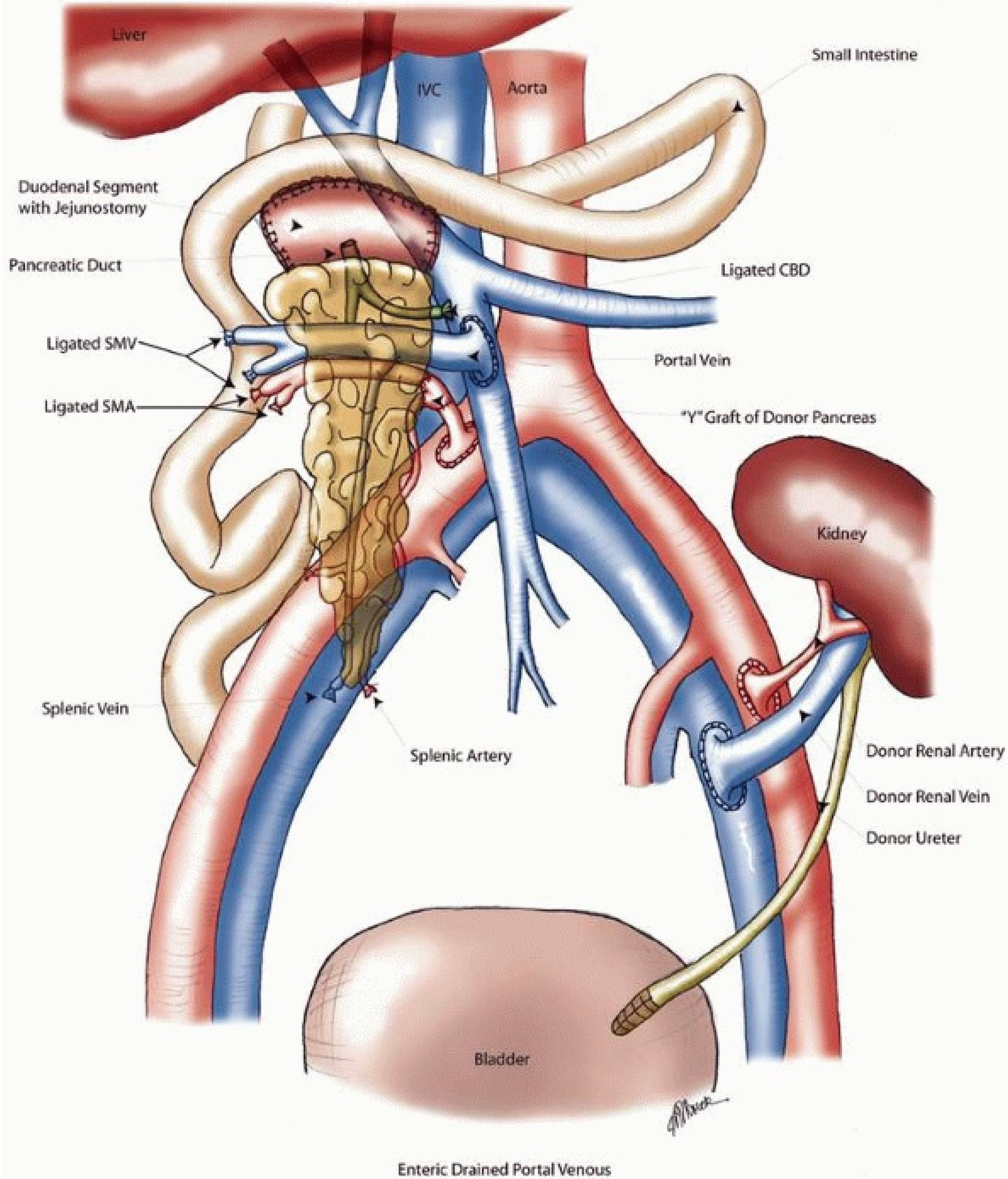


PLATE 15.4 Portal venous and enteric-drained pancreatic allograft with kidney on the left. SMA, superior mesenteric artery; SMV, superior mesenteric vein. (From Lipshutz GS, Wilkinson AH. Pancreas-kidney and pancreas transplantation for the treatment of diabetes mellitus. Endocrinol Metab Clin North Am 2007;36:1015-1038, with permission. see black and white image)

0-9

A

B

C

D

E

F

G

H

I

J

K

L

M

N

Editors: **Danovitch, Gabriel M.**
Title: ***Handbook of Kidney Transplantation, 5th Edition***

O

Editors: Danovitch, Gabriel M.
Title: *Handbook of Kidney Transplantation, 5th Edition*

P

Q

R

S

T

U

V

W

X

Editors: **Danovitch, Gabriel M.**
Title: ***Handbook of Kidney Transplantation*, *5th Edition***

Z